OEHHA RESPONSES TO PUBLIC COMMENTS ON:

DETERMINATION OF ACUTE TOXICITY EXPOSURE LEVELS FOR AIRBORNE TOXICANTS

and

EVALUATION OF ACUTE NON-CANCER HEALTH EFFECTS

The comments received by OEHHA included below are grouped alphabetically by commentator. The OEHHA response to each comment follows in separate paragraphs. Comments below were either directly transcribed from the original comments received, or were excerpted and summarized, as indicated.

Bay Area League of Industrial Associations

This set of comments supports several other referenced comments, the responses to which can be found under the respective primary sources.

Comment: We are concerned that OEHHA's methodology adds extra-conservatism to the RELs. This will have a real world effect on District air permitting decisions. We endorse the May 5, 1995 comments of the Santa Clara Valley Manufacturing Group on this topic. The acetone example in their comments is a realistic example of this concern. As we discussed in our meeting, Figure 2 on page 11 needs to have some language changed. We also suggest you consider their suggested revision to Table 1.

Response: The Technical Support Document (TSD) included acetone because it had clearly been shown to irritate the eyes and upper airways in acute and chronic human studies (Nelson *et al.*, 1943; Raleigh and McGee, 1972). Development of an REL for acetone made possible an analysis of worst-case scenarios involving modeled acute exposures, resulting in the conclusion that acetone does not pose a significant health hazard from single acute exposures. Without development of a health value for comparison, this analysis would not have been possible. As a result of the analysis, acetone has been removed from the list of 54 substances in the original acute TSD.

The comment is correct that the Figure 2 on page 11 is in error and this has been corrected in the revised draft to correspond with the text.

Comment: It is not appropriate to add the hazard quotient of criteria air pollutants in the background ambient air to the hazard quotients of compounds at the facility. This requirement for consideration of background "concentrations" is beyond the scope of AB 2588 and should be removed from the draft document.

Response: OEHHA has withdrawn the previous procedure of adding the criteria air pollutant effects to those of the non-criteria air pollutants.

California Cotton Ginners Association

The Association's main technical comments were the following:

Comment: As an example of the conservative procedures for developing the RELs for each of the chemicals, one should review the procedures used to develop an REL for Antimony Trioxide (Sb_20_3). The REL was based on a single study that indicated the presence of illnesses at a facility smelting antimony ore. While there may have been reported illnesses, OEHHA claims in Section IV. -page Antimony Trioxide - 2, that *"the effects of antimony alone cannot be deduced from this study because of concomitant exposure to other toxicants including arsenic."* However, OEHHA used the lowest measured concentration of antimony (0.40 mg/m^3) from this study to develop the REL. OEHHA then applied an uncertainty factor of 10 to estimate a No-Observed Adverse Effects Level (NOAEL) and another uncertainty factor of 10 to account for "intraspecies variability." OEHHA cites another study in the same section of the guidelines that "suggests that no adverse effects were observed following acute exposures to concentrations as great as 10 mg/m^3 Sb_2O_3 during 24 years of operations at one facility." We would suggest that each and every chemical be reevaluated and the uncertainty factors be eliminated.

Response: The acute REL for antimony trioxide is based upon the most appropriate data available. As in any complete review, OEHHA recognized and acknowledged the weaknesses of the cited study. Although the study noted concomitant exposure to arsenic, the level of arsenic exposure was low enough to support OEHHA's conclusion that the majority of the illnesses reported could be reasonably attributed to the antimony trioxide exposure. We have added a comment to the text to clarify this.

Regarding the reference by the commentator suggesting a NOAEL as great as 10 mg/m^3 Sb_2O_3, this reference was a presentation to the American Industrial Hygiene Conference in 1976. Unfortunately, as is noted in the reference section of the antimony trioxide acute toxicity summary, this reference was available only as a citation in NIOSH (1978) and is not available in the public scientific domain. While acknowledging the reference, OEHHA is compelled to base RELs on data that are available for review.

Regarding the use of uncertainty factors, this practice is well established (see TSD Section 3.3). Clearly, when the database available on a given chemical is as sparse as is the case for antimony compounds, uncertainty and data gaps exist. It is the responsibility of OEHHA to acknowledge and account for the unknowns as completely as possible using consistent methodology. In the case of antimony trioxide, uncertainty factors were applied to account for the lack of a clearly defined toxic threshold and to afford protection to sensitive individuals.

Comment: We adamantly oppose the inclusion of background emissions when the facility Hazard Index exceeds 0.5.

Response: OEHHA has withdrawn the previous procedure of adding the criteria air pollutant effects to those of the non-criteria air pollutants.

Comment: We would suggest that OEHHA revise the requirement to prepare and include an acute HI isopleth map, when the HI is greater than 0.5.

Response: OEHHA no longer suggests a specific HI.

California Mining Association

Comment: The commentator is concerned that the methodology outlined in the Guidelines will have a broad public policy impact on generators of airborne silica. The commentator is concerned that the proposed guidelines only permit companies to evaluate exposure limits for substances based upon information derived from animal studies and that human data are largely ignored.

Response: In response to the specific concerns about silica, it should be made clear that crystalline silica is not mentioned in these documents. In addition, throughout the Technical Support Document OEHHA has emphasized human data when such data were available and adequate. In fact, 33 of 45 REL values are based on human data. Only when human data are lacking or inadequate has OEHHA used animal data.

Chemical Industry Council of California

The Chemical Industry Council of California (CICC) offers the following comments on the Office of Environmental Health Hazard Assessment's draft "Evaluation of Acute Non-Cancer Health Effects, Part I" (December 1994). The focus of our comments, as supporters of the enabling legislation (SB 1731--Calderon, Chapter 1162, Statutes of 1992), are on OEHHA's misprioritization of its efforts in revising the state's health risk assessment for the Air Toxics Hot Spots program. In addition we contend, like many other commenting organizations, that OEHHA's use of two orders of magnitude in dealing with uncertainties and setting exposure levels for sensitive receptors is scientifically inappropriate.

CICC is the state trade association for chemical manufacturers, distributors and users. Its 89 member firms range in size from large California divisions of U.S. and worldwide companies to small family-owned facilities. The Council has been actively involved with the Hot Spots program since its passage in 1987 and has a vital stake in the regulatory framework that implements the program.

Comment: OEHHA has departed from the intent of SB 1731 by issuing acute noncancer guidelines. SB 1731 was an effort by industry to rectify scientific problems with health risk assessment guidelines issued by the California Air Pollution Control Officers Association (CAPCOA). As noted in the Assembly policy committee analysis, "The CAPCOA risk assessment guidelines have been criticized as being highly conservative and using unrealistic assumptions concerning exposure, toxic potency of chemicals, reliability of risk estimates and so forth." (Arnie Peters, Assembly Environmental Safety and Toxic Materials Committee, August 4,1992). The intent of the sponsors and supporters was to task OEHHA with revising the CAPCOA guidelines particularly with regards to the chronic exposures to cancer risks.

Response: The acute and chronic non-cancer, cancer, and exposure assessment guidelines and supplemental guidance are in preparation simultaneously. All of these guidelines are consistent with the letter and the intent of the original legislation. The acute non-cancer guidelines document, containing information on the smallest number of chemicals, was the first of these to be completed. OEHHA began working on the acute guidelines in 1989, three years before the passage of SB 1731. Two draft acute guideline documents were released for public comment in 1992, prior to the adoption of SB 1731. For these reasons, a draft acute guideline document for application to SB 1731 was prepared first. Documents describing the cancer and noncancer risks from chronic exposures have subsequently been released for public comment. A Technical Support Document on Exposure Assessment and Stochastic Analysis has been released for public comment as well. This last document was delayed in order to assemble an external advisory group composed of representatives of industry, academia, government, and environmental groups. The external advisory groups assisted OEHHA in an early step of preparing the document. This was necessary to help address the new field of stochastic analysis.

Comment: While the original statute (AB 2588 - Connelly, Chapter 1252, Statutes of 1987) was broad enough to cover both chronic and acute exposures, and cancer and noncancer health effects, the focus of the Hot Spots program during its initial implementation was on cancer risk, not on acute noncancer health effects. The Legislature found in Health and Safety Code Section 44301 (d) that "These [routine] releases may create localized concentrations or air toxic "hot spots" where emissions from specific sources *may expose individuals and population groups to elevated risks of adverse health effects, including, but not limited to, cancer* and contribute to the cumulative health risks of emissions from other sources in the area. . ." (Our emphasis in italics)

Response: The release of the acute non-cancer health effects document is consistent with the literal meaning of the italicized section above as well as the intent of the statute. Some of the key acute effects examined are birth defects and nerve damage, clearly important health effects. In addition, acute non-cancer health impacts can be life-threatening and long-lasting, and there are no existing federal guidelines or values to assist in the assessment of acute inhalation exposures, with the exception of the criteria air pollutants. The event that triggered California's Hot Spots Act, the New Jersey Toxic Catastrophe Prevention Act, and Federal SARA Title III was the Bhopal Incident in 1984, called by some the worst industrial accident in history. The release of methyl isocyanate, a toxic chemical not known to be carcinogenic, exposed at least 100,000 people to the plume of chemical, caused many thousands to suffer acute, chemically-induced injuries, many of which also had chronic effects, and resulted in at least 6000 deaths. This OEHHA document fills a badly needed gap for risk assessment. As stated above, the cancer risk portion of the guidelines is a concurrent project with the acute non-cancer guidelines, and have been subsequently released for public comment. OEHHA chose to release the documents as they were completed rather than waiting for a simultaneous release. OEHHA presented this concept at the public workshops held since August 1994. The early CAPCOA program focused on cancer risks due to the relative lack of health information on noncancer risks.

Comment: A review of the CAPCOA "Air Toxic 'Hot Spots' Program Risk Assessment Guidelines (January 1991) reveals that the implementing jurisdictions focused on doing health risk assessments at high priority facilities to identify cancer risks, not on acute noncancer health effects. OEHHA notes this distinction in its Introduction where it discusses an inability to achieve uniformity in risk assessment methodology across various programs that deal with accident scenarios (Business Inventory Plans, Hazwoper, RMPPs).

Response: The CAPCOA guidelines <u>also</u> contained one-hour RELs for thirty two chemicals. These have been used in risk assessments for Hot Spots facilities. Therefore, this is not a new procedure. If additional acute RELs had been available when the CAPCOA guidelines were prepared, they would have been included. Discussion of accidental release activities has been substantially edited to reduce confusion and provide a clearer focus on the Hot Spots Program activities.

Comment: Since Health and Safety Code Section 44360 (b) (2), which governs OEHHA's role in development of risk assessment guidelines, does not prioritize which guidelines to issue, the

controlling mechanism in this case should be the bill's intent as cited in the committee analysis. In straying from this direction OEHHA has raised the question of why it chose to issue acute noncancer health effects guidelines first.

Response: OEHHA has not strayed from the intent of the bill. The schedule for release was first discussed at the scientific review panel meeting in May, 1995, and at subsequent public workshops. The acute non-cancer guidelines document, containing information on the smallest number of chemicals, was the first completed because OEHHA began working on it three years before passage of SB 1731. OEHHA has now completed drafts of the other three technical support documents and released them for public comment. Our intent was to complete all the documents expeditiously, but due to resource reductions and technical difficulties in preparing some of the documents, they could not all be released at the same time.

Comment: OEHHA has ignored the statutory requirement to issue guidance for submission of supplemental information.

A review of Part I and Part II of the draft documents does not reveal any guidance for inclusion of supplemental information to the health risk assessment as called for in H & SC Section 44360 (b)(3)(A) - (D). Given the concern about OEHHA's methodology and use of conservative margins of safety, the lack of guidance is a serious oversight that should be corrected.

Response: The inclusion of supplemental information as outlined in H & SC Section 44360(b)(3) focuses on "probabilistic" or "likelihood" analyses. The fourth section of these guidelines, Exposure Assessment and Stochastic Analysis, which was released in December 1996, deals with a probabilistic approach to exposure assessment. OEHHA is responsible for preparing health risk assessment guidance, which includes dose-response assessment and basic exposure assessment as well as supplemental guidance.

Comment: Proposing new risk assessment guidelines that are not uniform undermines the risk assessment review process required by SB 1082 (Calderon).

Subsequent legislation by Senator Calderon, the author of SB 1731, requires a comprehensive review of all risk assessment methodologies within Cal/EPA. The intent of the statute is to bring some uniformity, and hence cost effectiveness, to the risk assessment process. The issuance of new acute noncancer health effects risk assessment guidelines, while long delayed, comes before the Risk Assessment Advisory Committee can do its review and make recommendations on whether sound scientific knowledge, methods and practices are being utilized and whether any departure from National Academy of Science and U.S. EPA practices are appropriate. The downstream potential for revision of these guidelines, and the related cost, is revealed in OEHHA's comments on its inability to achieve uniformity with other risk assessments.

Response: OEHHA's SB 1731 mandate was started before SB 1082. OEHHA therefore has been working on these guidelines well before a Risk Assessment Advisory Committee was

assembled. The Air Resources Board's Scientific Review Panel is charged with reviewing guidelines that result from OEHHA's SB 1731 activities. Some of the SRP members were also on the SB 1082 committees. Where guidelines were available, OEHHA did not depart from the practices of NAS and USEPA. The U.S. EPA's Science Advisory Board stated that noncancer risk assessment is among the most important future challenges to the Agency. It is expected that the guidelines will bring significant uniformity in the risk assessment process. The current revisions of the acute document reflect concerns of the Risk Assessment Advisory Committee. The current version reflects a number of reduced uncertainty factors due to an improved understanding of the database. The issue of severity of effect raised by the RAAC was addressed by reducing a number of LOAEL to NOAEL uncertainty factors for less severe effects.

The commentator confuses the lack of uniformity in emergency release guidance pointed out by OEHHA with "inability to achieve uniformity with other risk assessments." The Hot Spots program does not involve emergency releases.

Comments: OEHHA is creating a new mission for itself and contributing to California's competitive disadvantage.

By issuing new, highly conservative risk assessment guidelines for acute exposures instead of chronic exposures to "Hot Spots" listed chemicals, OEHHA will force most air districts to reevaluate the scope of their AB 2588 program and potentially require high priority facilities to submit new or revised health risk assessments. Because Reference Exposure Level I values are set so conservatively, other facilities may be brought into the program and required to do a health risk assessment. The effect of this action is to sustain the air toxics hot spots program at current or increased levels, even though it has reached maturation and in many cases led to the reduction of emissions of listed chemicals.

Response: This document is only one of four technical support documents. Part II deals with cancer potency factors and Part III describes chronic noncancer reference exposure levels. Since the RELs in this guidance are based on the best available science, and since benchmark dose methodology has been incorporated into the methodology for determining RELs, this document is the most comprehensive source of information on dose-dependent acute inhalation health effects for use in the general population. Because of resource limitations, most of the 450 chemicals for which emissions must be quantified did not have acute RELs derived. When the CAPCOA guidelines were prepared and revised it was acknowledged that new information would result in updates and revisions. OEHHA is following the mandate to develop health risk assessment guidelines that incorporate margins of safety (AB 2728, Statutes of 1992, Chapter 1161 HSC Section 39660), and has not created a new mission or mandate. The guidelines contain the best available information to conduct a comprehensive health assessment of Hot Spots facilities. The current CAPCOA guidelines include acute exposure risk assessments. If some districts have not followed the guidelines in this area, then they may not have considered an important area of health impacts from stationary sources.

Comment: The fee requirement in HSC Section 44380 that supports OEHHA review activity will be an ongoing source of revenue for the office based solely on artificially conservative margins of safety. This effect is compounded by the fee authority in Section 44380.5, added by SB 1731, which permits a review authority to assess an amount to cover the cost of reviewing the supplemental information submitted by facilities in their health risk assessments. Conservative margins of safety will no doubt force many facilities to submit supplemental information and thus trigger the fee.

Response: OEHHA is mandated to derive risk assessment RELs that are protective of public health. Margins of safety, by definition, account for vast areas of uncertainty in the distribution of toxicological responses in the human population. When large areas of uncertainty exist in the toxicological database, as is the case for the majority of chemicals, it is necessary to err on the side of safety. Based on scientific presentations made at the 1997 Society of Toxicology meeting, a factor of ten in one area of uncertainty is protective of 80 to 90% of the population (Stickney JA, Keenan RE, and Swartout JC. 1997. A probabilistic framework for the Reference Dose. Abstract #1054). Two factors of ten are protective of 95 to 99% of the population. Thus, the current practice appears to be justified from a scientific perspective as well. Where possible, we have used human data which minimize uncertainty and reduce uncertainty factors (e.g., the chlorine and sulfuric acid RELs have UFs of 1). Most of the RELs in this document (33 of 45) are based on human data. Furthermore, we have proposed a benchmark dose methodology which reduces uncertainty by using the dose-response information from a given data set. As a result, the overall uncertainty factor for individual variation has been reduced from 10 to 3. Similarly, RELs based on LOAELs for mild sensory irritation, have reduced uncertainty factors of 3 instead of the traditional 10. OEHHA has incorporated the best available scientific information into the traditional uncertainty factor method where data have allowed such a departure to occur without endangering community health. The methodology used to develop reference exposure levels is independent of the funding mechanism for the Air Toxics Hot Spots Program.

Comment: Sustaining a regulatory program that has reached maturity and accomplished many of its public health safety goals at artificial levels through new fees adds to the competitive disadvantage suffered by California businesses.

Response: The development of RELs is entirely independent of the development of the Air Resources Board's fee regulation for the Air Toxics Hot Spots Program. The RELs are not "artificial" but are based on the best available scientific health effect information.

Comment: OEHHA's margins of safety are too conservative and outside the scientific mainstream.

Draft document Part II references AB 2728 (Tanner, Chapter 1161, Statutes of 1992) which administratively added the list of federal hazardous air pollutants to California's air toxic contaminants list and required that "ample margins of safety" for exposures be set. Data from a wide selection of authoritative bodies was required to be reviewed.

OEHHA has chosen not to use existing reference exposure levels in U.S. EPA's Integrated Risk - Information System database and calculated its own RELs. As noted by many of the Chemical Manufacturers Association CHEMSTAR Panels in their comments, OEHHA has been overly conservative in setting margins of safety to account for uncertainties in the data and to protect sensitive receptors. OEHHA chose a factor of 10 for both calculations where current scientific, thinking, as referenced in the National Research Council's Guidelines for Developing Community Emergency Exposure Levels, considers a factor of three (3) for uncertainty and a factor of two (2) for sensitive receptors to be appropriate. OEHHA has substituted a risk management policy choice for a scientific risk assessment choice.

Response: The USEPA IRIS values referred to in the comment are not for acute inhalation exposures, but are for long-term chronic exposures. If OEHHA adopted the chronic values for acute exposures, the reference levels would suggest much greater risks because the USEPA IRIS values are for chronic exposure and are therefore lower than the proposed OEHHA values. It would therefore be inappropriate and scientifically unsound to use IRIS values for acute reference exposure levels. There are presently no existing standards for acute inhalation exposure of chemicals by USEPA, with the exception of the criteria air pollutants. Regarding the magnitude of uncertainty factors, the NRC explicitly states in their executive summary (NRC, executive summary, pg. 6) that *"It is vital to select uncertainty factors that reflect the quality and relevance of the data, differences between test species and humans, and variation within the human population. Typically, in the past the permissible human exposure has been reduced by a factor of 10 for each additional source of variation or uncertainty."* In cases where specific information existed on sensitive individuals, OEHHA used smaller uncertainty factors. For example, the sulfuric acid REL has a UF of 1, since the study forming the basis of the REL was conducted on individuals with asthma, and since a fair amount of data exist on the acute respiratory effects of sulfuric acid in these individuals. OEHHA has included consideration of severity of effect, in accordance with the RAAC committee recommendations, by reducing uncertainty factors in those cases where the adverse effect is mild sensory irritation.

Comment: The net result is typical for California -- exposure levels that are far more conservative than other standards established by authoritative bodies. Lower standards translates into more compliance costs for California businesses.

Response: There are no other existing reference exposure levels for acute exposures to compare with OEHHA's RELs. The values published by other organizations (AIHA, ACGIH, NAS) have been reviewed and included into the Technical Support Document when appropriate. As stated above, the RELs have been derived objectively, and with margins of safety that are reduced in cases where scientifically valid reasons allowed departure from defaults.

(In April 1998 USEPA released an External Review Draft titled Methods for Exposure-Response Analysis for Acute Inhalation Exposure to Chemicals. Development of the Acute Reference Exposure. USEPA identifies acute as less than 24 hours and estimates Acute Reference Exposures (AREs) for several durations less than 24 hours as compared to OEHHA's 1 hour

duration. USEPA uses two methods which OEHHA uses (NOAEL/uncertainty factor and benchmark dose) and a third, very data intensive method named categorical regression. USEPA's ARE seems similar to OEHHA"s Level I acute REL. Since USEPA presents an ARE derivation for only 3 chemicals, one calculated by each method, there is little to compare. In the one comparison possible USEPA derived by categorical regression an ARE of 87 $\mu g/m^3$ for hydrogen sulfide while OEHHA developed a Level I REL of 140 $\mu g/m^3$ for 1 hour using the NOAEL/uncertainty factor approach.)

Comment: OEHHA should more directly respond to the intent of SB 1731 by revising the chronic health risk assessment guidelines first. The draft acute noncancer health effects guidelines should be withdrawn from consideration at this point. Consideration should be given to coordinating any new health risk assessment guidelines with the review being conducted by the Risk Assessment Advisory Committee in order to maximize uniformity among risk assessments. OEHHA should review its policy regarding margins of safety with the intent of aligning itself with current scientific thinking on the federal level so that public safety is protected while California businesses do not continue to be placed at a competitive disadvantage.

Response: As previously stated, we believe that the acute noncancer health effects are an integral part of the Hot Spots Program. However, in part due to other comments, the acute document was placed on hold until the other Technical Support Documents could be completed, and issues raised by the RAAC could be incorporated. Now that the other documents have been released for public comment, and the document has been revised to reflect issues raised by the RAAC, the process is proceeding. Since no federal acute RELs exist, it is not possible for OEHHA to be aligned with existing federal methodology at this time. OEHHA staff are working with USEPA staff to assist them in their acute guidance development process, which has now begun.

Chemical Manufacturers Association

The following are comments regarding benchmark dose methodology.

Comment: Estimation of benchmark doses has been suggested as an alternative and preferred methodology to Using No Observed Adverse Effect Levels (NOAELs) or Lowest Observed Adverse effect Levels (LOAELs) in setting "safe" levels of exposure for humans to materials known to cause non-cancer toxic effects in laboratory animals, at least at sufficiently high doses. California's Office of Environmental Health Hazard Assessment (OEHHA) has proposed an application of the benchmark dose methodology for use in setting regulatory levels, specifically Reference Exposure Levels (RELs) under the Air Toxic "Hot Spots" Information and Assessment Act of 1987. In general, the Chemical Manufacturers Association (CMA) is supportive of the benchmark dose methodology, when executed properly. We have a number of serious concerns with the benchmark dose methodology proposed by OEHHA for setting acute toxicity exposure levels for airborne toxicants. These concerns include the following:

OEHHA should acknowledge explicitly that without incorporation of information regarding specific mechanisms of toxic action, the benchmark dose approach is little more than mathematical curve-fitting. Therefore, modeling should stay within the observable range (e.g. 10% effect) and not attempt to extrapolate as low as a 1% effect level.

Response: Unless the study is well-designed, with a 0% response, it is difficult to estimate the toxic effect threshold without going below the observable range. The observable range varies among data sets. In estimating a practical threshold for effects in the study population, it is usually necessary to extrapolate below the observable range since the sample sizes are frequently very small, particularly in the case of acute exposure data. In accordance with the published consensus of the Benchmark Dose Workshop (Regul. Toxicol. Pharmacol. 21:296-306, 1995), OEHHA is adopting the benchmark concentration for a 5% effect (BC_{05}) as an acceptable benchmark concentration instead of the BC_{01}. In addition, recent analyses by OEHHA staff have supported use of the BC_{05} as an effective substitute for the semi-quantitative NOAEL approach. The benchmark dose calculations in the Technical Support Document have been changed to reflect this.

Comment: There is a clear need to thoroughly explore and identify the types of "pathological" data sets from which inappropriate or invalid benchmark dose estimates may result. In particular, sensitivity analyses of the influence of high dose observations of the benchmark dose estimates should be undertaken.

Response: In most cases, the number of dose groups is a limiting factor in benchmark dose calculations, therefore there are few opportunities to discard any of the groups. When multiple high dose groups exist beyond a peak response, the highest doses are not included. All benchmark dose calculations performed by OEHHA using the probit model must meet a Chi-Square test for goodness of fit ($p > 0.05$). In addition, benchmark doses that appear

contradictory to other experimental data have been noted and have not been used (see life threatening effect level calculation for ammonia in the Technical Support Document).

Comment: Demonstrations that benchmark dose estimates are not idiosyncratically sensitive to the choice of a specific dose-response model should be presented. A variety of models should be selected in order to demonstrate that the outcome is insensitive to the model choice.

Response: The use of multiple models may be useful as a quality control measure for the benchmark dose calculation. The Weibull model, which tends to yield slightly lower estimates at low doses, can be used for this purpose. However, although we compare the results of log-normal and Weibull models, we do not believe that addition of multiple models to each calculation is useful for inclusion into the Document. There was little effect by model choice for extrapolation down to BC_{01} in the analysis conducted by Crump (1983) for acute effects. OEHHA suggests using the log-normal model, due to recent analyses (Fowles and Alexeeff, 1996) that indicate it generally provides a better fit to the acute data than the Weibull model.

Comment: A thorough and objective evaluation of OEHHA's methodology for developing maximum likelihood and lower bound estimates of probit model benchmark doses should be provided.

Response: OEHHA agrees with the commentator's point. OEHHA prefers to make public all software used in the generation of risk assessment values. However, the only software presently available for this calculation is currently protected by proprietary laws. We have checked the performance of the Probit model software by Crump against in-house calculations, and with newer programs created by ICF-Kaiser Co. (Ruston, LA; Tox-Risk v.3.5) and these have given similar results. Therefore, we believe that this software is accurate in determining maximum likelihood estimates and lower bounds. In any case, OEHHA's calculations are based on a probit extrapolation, thus any model that makes a proper probit extrapolation and maximum likelihood lower bound estimate can be used.

Comment: Point and lower bound benchmark dose estimates should be compared to the NOAELs and/or LOAELs that could have been obtained with conventional safety assessment methods from the same toxicology studies. This will permit a simple and direct assessment of the degree of additional conservatism, if any, that is introduced by OEHHA's proposed approach relative to the more traditional one.

Response: Benchmark dose estimates do not need to be compared to NOAEL/uncertainty factor estimates on a case by case basis. The value of the benchmark dose is independent of its relation to a specific NOAEL estimate. Our previous analysis (Fowles and Alexeeff, 1996) has indicated that "extra-conservatism" is an unwarranted concern for benchmark calculations (e.g., BC_{05} and BC_{01}) for acute inhalation data, using NOAELs and LOAELs as a guide. No justification has been presented to support the reasoning that a large difference between a NOAEL and a

benchmark dose estimate is sufficient reason to discard the benchmark analysis. However, in cases where the benchmark analysis clearly contradicts existing data, care and judgment must be used in selecting the appropriate method for REL estimation. It is the purpose of the benchmark dose to reduce uncertainty in estimating thresholds for the onset of toxic effects by improving our understanding of dose-response relationships. Thus, a changed magnitude of the reference value does not necessarily reflect "conservatism" or lack thereof, but may in fact reflect improved understanding of the dose-response relationship.

Comment: The benchmark dose approach employing the Weibull model appears to linearize the low dose response for non-cancer endpoints, and similar results may ensue from use of the Probit model as has been proposed by OEHHA. There is a critical need to determine and document the performance characteristics of this procedure with regard to low-dose linearity because it may inappropriately add conservatism to benchmark dose estimates. The response in this region should be better characterized before it is adopted for use in regulatory decision-making.

Response: The vast majority of acute toxicity studies use small sample sizes and few experimental groups. For these reasons, these models often extrapolate to lower doses and response rates than those observed in the experimental studies. However, standard "low-dose extrapolation", several orders of magnitude below the data, does not occur in benchmark dose calculations. An empirical comparison of the BD_{05} from Probit and Weibull models shows similar but slightly lower values when using the Weibull model. Whether a linear extrapolation to low doses is appropriate or not is an issue that can only be addressed in the context of specific experimental data, which usually do not exist. We have endeavored to show the raw data in addition to a graphic display of each benchmark dose calculation in the Technical Support Document, thus documenting and illustrating the modeled relationships. When extrapolating to a level of BC_{01} or BC_{05} the choice of model has little impact on the result according to Crump (1983). However, the log-normal model was superior to the Weibull model using goodness of fit criteria, number of data sets amenable to analysis, and minimizing variance in relation to respective NOAELs. Consequently, the log-normal model was chosen for acute benchmark dose estimations.

Chemical Manufacturers Association (specific panels)

Acetone Panel

Comment: Acetone should not be regulated as an air toxic. Acetone is not listed as a hazardous air pollutant under the federal Clean Air Act and the United States Environmental Protection Agency has proposed to remove acetone from the list of toxic chemicals under Section 313 of the Emergency Planning and Community Right-to-Know Act. Acetone also has negligible photochemical reactivity, and EPA has proposed to classify it as a non-VOC (volatile organic compound). EPA has listed acetone as an acceptable substitute for ozone-depleting substances in several applications. Acetone is naturally present at detectable levels in most tissues and fluids of the human body.

Response: Hazard is a function of toxicity and exposure. If the toxicity is low and the exposure is low, then the hazard will be low. However, the toxicity of the substance and the REL would remain unchanged. In this case, the toxicity of acetone is low, and the modeled exposures indicate that it would not pose any significant health risk, even in worst-case scenarios. Based on this information, acetone has been removed from the list of Hot Spots chemicals by the Air Resources Board.

Comment: An uncertainty factor of 10 is not necessary to protect sensitive subpopulations from the effects of mild eye, nose and throat irritation. No uncertainty in rate of metabolism is involved, thus lowering intraspecies variability.

Response: As stated above, acetone has been removed from the list of Hot Spots chemicals by the Air Resources Board.

Comment: The proposal inappropriately includes eye, nose and throat irritation with other types of respiratory tract irritation that involve different mechanisms of action and severity of effect.

Response: According to the comment, only chemical toxicities with the same mechanisms should be summed in a hazard quotient. However, most chemicals have multiple mechanisms of toxicity and regions of effect in the lung. Because of this OEHHA has suggested designating the respiratory system as a target, rather than speciating each cell and tissue type separately and without delineating various regions of the lung as separate target sub-sites. The result is a simplified approach that does not assume exclusivity about the region of effect in the respiratory tract of a chemical simply because data gaps prevent a more precise estimation of the chemical's effects. Additionally, multiple indirect influences on organ physiology cannot be disregarded simply because the molecular or cellular targets of two chemicals are not identical. For example, one chemical may influence the toxicity of another chemical by inducing metabolic enzymes or by decreasing intracellular glutathione, even though the "mechanism" of toxicity of the two chemicals may be quite different. We believe that we have been consistent in categorizing severity of effect as described in the introduction section of the technical support document.

Comment: OEHHA should remove the references in the toxicological summary to the Nizyaeva study (1982) that states that acetone is a developmental and reproductive toxicant. This study is of questionable validity, and its inclusion in the summary gives the public the erroneous impression that acetone is a highly toxic chemical.

Response: OEHHA agrees that the Nizyaeva study may be of questionable utility. However, in absence of any other more reliable information specific to certain endpoints, it is prudent to at least mention these data. The Air Resources Board has removed acetone from the list of toxic substances. Additional research into the reproductive toxicity of acetone could help resolve this issue.

Comment: OEHHA's conservative reference exposure level (REL) for acetone has practical negative consequences for industrial facilities, the public and regulatory agencies. The program will impose substantial costs on industrial facilities and local Air Quality Management Districts with little risk reduction benefit. The program may have a negative impact on pollution prevention by discouraging companies from using acetone, which has negligible photochemical reactivity and relatively low toxicity. Companies may switch to more toxic chemicals.

Response: Acetone has been removed from the list of Hot Spot substances by the Air Resources Board, for reasons previously discussed. The REL that was previously proposed was instrumental in determining that a negligible risk existed from acute airborne exposures to acetone.

Several agencies, including the U.S. EPA, NAS, ACGIH, and ATSDR have health-based standards for acetone (RfD, EEGL, TLV, and MRL, respectively). The ACGIH-TLV itself is based on mild irritation (ACGIH, 1991). Nevertheless, OEHHA has withdrawn acetone from the TSD.

References:

Nelson KW, Ege JF, Ross M, Woodman LE, Silverman L. Sensory response to certain industrial solvent vapors. J Ind Hyg Toxicol 1943;25(7):282-285.

Raleigh RL, McGee WA. Effects of short, high-concentration exposures to acetone as determined by observation in the work area. J Occup Med 1972;14(8):607-610.

Carbon Disulfide Panel

The Panel's main comments were the following:

Comment: OEHHA is urged to revise its risk assessment methodology which is overly conservative and results in the calculation of misleadingly low values.

Response: The methodology proposed by OEHHA is consistent with the NRC Guidelines (1993) and with USEPA's methodology. Areas of uncertainty are accounted for through use of uncertainty factors. The NRC explicitly states in their executive summary (NRC, executive summary, pg. 6) that *"It is vital to select uncertainty factors that reflect the quality and relevance of the data, differences between test species and humans, and variation within the human population. Typically, in the past the permissible human exposure has been reduced by a factor of 10 for each additional source of variation or uncertainty."* In cases where specific information existed on sensitive individuals, OEHHA used smaller uncertainty factors. For example, the sulfuric acid REL has a UF of 1, since the study forming the basis of the REL was conducted on individuals with asthma, and since a relative wealth of data exist on the acute respiratory effects of sulfuric acid in these individuals.

Comment: OEHHA is urged to Revise its proposed Level II for carbon disulfide of 0.98 ppm, which was set without reference to major recent animal studies addressing reproductive and developmental toxicity. These studies would support the calculation of a Level II value of at least 7.3 ppm or 6.1 ppm, even using OEHHA's overly conservative current methodology.

Response: OEHHA has reviewed recent animal reproductive toxicity presented in the attachment to the comment and has reevaluated the severe adverse effect level accordingly. Please note the change to the carbon disulfide toxicity summary for discussion of studies and calculation of a severe adverse effect level based on these data. OEHHA thanks the commentator for the contribution to the TSD by the submission of additional toxicological information.

Comment: OEHHA is urged to not to use a 100-fold uncertainty factor for establishing the carbon disulfide Level II value.

Response: The paper by Dourson and Stara (1983) suggests that a 10-fold uncertainty factor is appropriate for intraspecies uncertainty. This point is summarized on page 228 of that paper: *"From this brief presentation of data it seems somewhat reasonable to employ a 10-fold uncertainty factor to account for intraspecies variability in lieu of chemical-specific toxicity data."*.

Similarly, using the attached information provided by Monsanto (Nair *et al*., unpublished data, 1989), it is clear that an uncertainty factor of 3 for interspecies variability does not provide an adequate margin of safety in many situations. For example, in Figure 2 of their attachment, comparing mice and dogs, an interspecies UF of 3 would only be adequate in 17/30 cases, or 56%

of the time. A comparison between rodents and humans would likely show even greater discrepancies due to greater differences in body weight, metabolism, toxicokinetics, activity patterns, excretion, and other factors.

For reasons discussed above, uncertainty factors of 10 appear to be adequate to account for inter- and intraspecies differences in the absence of chemical-specific data.

Comment: OEHHA is urged to revise its discussion of the Hemminki and Niemi (1982) study, which is inadequate for drawing any conclusions regarding carbon disulfide toxicity.

Response: In response to this comment, the discussion of the Hemminki and Niemi (1982) study has been modified in the technical support document.

Comment: OEHHA is urged to revise its discussion of the Zenick *et al*. study.

Response: In response to this comment, the discussion of the Zenick *et al*. study has been modified in the technical support document.

Comment: OEHHA is urged to adopt the American Industrial Hygiene Association's Emergency Response Planning Guidelines (ERPG)-1 level of 1 ppm for the Level I value, based upon odor. The Panel notes in this regard that odor is not an adverse health effect. The 1 ppm level thus would not relate to an adverse health effect.

Response: We agree with the commentator that odor detection may not be an adverse health effect. We also believe that an REL based on the odor threshold data used as the basis of the ERPG-1 is inappropriate. After reviewing the AIHA-ERPG-1 and the odor threshold data also presented by AIHA (1989), OEHHA determined the ERPG-1 to be an inadequate basis for a Level I REL. The AIHA-ERPG committee cites an odor threshold of 0.21 ppm as the basis for the ERPG-1 of 1 ppm. This value is referenced as ASTM (1973), which is a compilation of available odor threshold data; the original source for this odor threshold is Leonardos (1969). However, AIHA (1989), in a critical review of odor threshold data, rejects the use of the 0.21 ppm threshold because this value represents a 100% recognition concentration. The AIHA-ERPG-1 of 1 ppm is consequently nearly five times greater than the reported 100% recognition threshold data rejected by AIHA (1989).

References:

American Industrial Hygiene Association (AIHA) Odor thresholds for chemicals with established occupational health standards. Akron (OH): AIHA; 1989. p. 14, 50.

American Society for Testing and Materials (ASTM). Compilation of odor and taste threshold values data. Stahl WH, editor. Philadelphia: American Society for Testing and Materials; 1973. p. 105.

Ethylene Glycol Ethers Panel

The comment's main points were the following and concern EGBE:

Comment: The Panel wishes to bring to your attention toxicity information concerning ethylene glycol butyl ether that indicates the proposed acute toxicity reference exposure level (REL) for this chemical should be increased. First, a NOAEL irritation level has recently been demonstrated in humans by Johanson and Boman, who exposed volunteers to 50 ppm for two hours without reporting any irritation (or any systemic toxicity). "Percutaneous Absorption of 2-Butoxyethanol Vapour in Human Subjects," Br. J. Ind. Medicine, 48:788-792 (1991). Second, an uncertainty factor of 10 for acute effects in potentially sensitive individuals is unduly large. The OSHA PEL for EGBE has for many years been 50 ppm (although this was reduced to conform to the ACGIH TLV of 25 ppm for a few years). No reports of irritation have occurred under these limits.

Response: Based on reevaluation of the literature, the key reference and the endpoint for the REL for EGBE has changed. The most sensitive endpoint for EGBE is reproductive toxicity. The REL is based on reduced gravid uterine weight, reduction in total fetuses, fewer viable fetuses, increased maternal deaths, increased spontaneous abortions, and decreased body weight in rabbits, as reported by Tyl *et al*. (1984). Human sensory irritation data for EGBE identify NOAELs and LOAELs that are not protective of the potential reproductive toxicity described above.

Comment: Although the Level II and Level III findings will not be employed by California (given the existence of a Level I value), both values fail to reflect the substantial database indicating man is much less susceptible to hemolytic effects than rats and mice. Given these failings, we urge OEHHA not to issue Level II or Level III RELs for EGBE.

Response: The rat LOAEL was originally used as it was the lowest LOAEL reported in the study. However, to more accurately reflect data indicating that rats and mice are more sensitive to hemolysis following EGBE exposure, the severe adverse effect level has been revised.

While it is well characterized that rats and mice are more sensitive than humans to the hemolytic effects of EGBE, toxicity has been shown in species that did not exhibit signs of hemolysis. Tyl *et al*. (1984) reported rabbit data indicating the occurrence of embryotoxicity and maternal toxicity unrelated to hemolysis. Data on embryotoxicity and maternal toxicity, while not synonymous with developmental toxicity, provides compelling evidence of non-hemolysis toxicity. For the previous reasons, data on toxicity of EGBE in pregnant rabbits provide the basis for the revised Level II.

Although Udden *et al*. (1994) clearly demonstrated that human subpopulations with hemolytic disorders were not more sensitive to the hemolytic effects of EGBE, the variability in human responses has not been completely characterized. Because the mechanism for rabbit maternal toxicity and embryotoxicity is unclear and because the true range of human responses is uncharacterized, an UF of 10 is used.

The life threatening effect level has been withdrawn and lethality data from a guinea pig, a species less sensitive than the rat to EGBE, has been added to the body of the summary.

References:

Carpenter CP, Pozzani UC, Weil CS, Nair JH, Keck GA, Smyth HF. The toxicity of butyl cellosolve solvent. Arch Ind Health 1956;14:114-131.

Ghanayem BI, Ward S, Wall C. Effects of 1-butoxyethanol (BE) and its toxic metabolite, 2-butoxyacetic acid (BAA) on blood from various mammals in vivo and in vitro [abstract]. Toxicologist 1992;12, 282.

Johanson G, Boman, A. Percutaneous absorption of 2-butoxyethanol vapour in human subjects. Br J Ind Med 1991;48:788-792.

Tyl RW, Millicovsky G, Dodd DE, Pritts IM, France KA, Fischer LC. Teratologic evaluation of ethylene glycol monobutyl ether in Fischer 344 rats and New Zealand white rabbits following inhalation exposure. Environ Health Perspect 1984;57:47-68.

Udden MM. Hemolysis and deformability of erythrocytes exposed to butoxyacetic acid, a metabolite of 2-butoxyethanol: II. Resistance in red blood cells from humans with potential susceptibility. J Appl Toxicol 1994;14(2):97-102.

Udden MM, Patton CS. Hemolysis and deformability of erythrocytes exposed to butoxyacetic acid, a metabolite of 2-butoxyethanol. I. Sensitivity in rats and resistance in normal humans. J Appl Toxicol 1994;14(2):91-96.

Werner HW, Mitchell JL, Miller JW, Von Oettingen W.F. The acute toxicity of vapors of several monoalkyl ethers of ethylene glycol. J Ind Hyg Toxicol 1943;25:157-163.

Isopropanol Panel

The main concerns expressed in the comments were the following:

Comment: Isopropanol should not be regulated as an air toxic. Isopropanol is not listed as a hazardous air pollutant under the federal Clean Air Act, nor is it listed on Section 313 of the Emergency Planning and Community Right-to-Know Act. Isopropanol has relatively low toxicity and low photochemical reactivity, and does not pose significant risks to human health or the environment.

Response: OEHHA does not regulate chemical use. We are simply providing information on health effects of chemicals subject to the Hot Spots statute. The available human and animal data indicate that isopropanol is generally of low systemic toxicity, but irritation and CNS effects have been observed. Reasonable indicators of irritation include laboratory animal RD_{50} values and evidence of reversible damage to the olfactory epithelium in guinea pigs. Furthermore, more recent data (Gill *et al*., 1995) describe the transient neurotoxic effects of isopropanol exposure. Therefore, while long term local or systemic injury following short-term exposure is unlikely, the compound is not without toxicity. OEHHA agrees that isopropanol may be a viable alternative to compounds with greater systemic toxicity and photoreactivity. However, the volume of isopropanol released is very large. For this reason alone, the potential toxicity of this compound warrants consideration.

Comment: OEHHA's proposed one-hour reference exposure level (REL) for isopropanol is 2000 times lower than the American Conference of Governmental Industrial Hygienists (ACGIH) 8-hour threshold limit value (TLV), 2500 times lower than the ACGIH 15-minute short term exposure limit (STEL), and 100 times lower than the odor threshold for isopropanol. In addition, the proposed REL for isopropanol is -approximately the same as the proposed REL for nitrogen dioxide, even though ACGIH TLVs show that nitrogen dioxide is at least 100 times more acutely toxic than isopropanol. As a result of these inconsistencies, the REL for isopropanol lacks technical credibility.

Response: OEHHA recognizes the proposed REL for isopropanol is lower than other published values. However, the levels developed in the technical support document should be based on identifiable toxicity studies. We have considered the information provided in the comments and concluded that the proposed REL should be changed based upon the comments received.

Comment: OEHHA should modify its derivation of the REL for isopropanol to ensure a technically credible result. Specifically, OEHHA should not consider mild eye, nose and throat irritation to be an "adverse" effect for regulatory purposes. As a result, 400 ppm should be considered a no adverse effect level (NOAEL), not a lowest observed adverse effect level (LOAEL). At the very least, OEHHA should consider 200 ppm, based on the Nelson study, to be a NOAEL. The Nelson study states that a majority of tests subjects concluded that exposure to 200 ppm isopropanol would be satisfactory for 8 hours, and no irritation was reported at that

level in any test subjects. OEHHA staff toxicologists have expressed uncertainty concerning whether the test subjects of the Nelson study were actually exposed to 200 ppm isopropanol. The Panel believes, however, that the better reading of the Nelson study is that subjects were exposed to 200 ppm isopropanol.

Response: OEHHA disagrees with the commentator and believes that mild eye, nose, and throat irritation is an adverse health effect. The consideration of mild eye, nose and throat irritation as adverse effects has been undertaken by other organizations concerned about chemical exposures as well. For example, the ACGIH-TLV for isopropanol, a published value to which the REL is compared in the comment, is "set on the basis of eye, nose and throat irritation" (ACGIH, 1991). Regarding the Nelson human exposure study, OEHHA has reevaluated its interpretation and agrees with the comment that, even though it is not clear the subjects were actually exposed to isopropanol at 200 ppm, a NOAEL of 200 ppm can be concluded from the study since the subjects indicated that prolonged exposure to 200 ppm would be tolerable. Therefore, the RELwas reevaluated using a NOAEL of 200 ppm. The REL has been changed from 490 to 3200 $\mu g/m^3$.

Comment: OEHHA proposes to use an uncertainty factor of 10 to extrapolate from a LOAEL (based on mild irritation) to a NOAEL; an uncertainty factor of 10 to protect sensitive subpopulations; and a factor of 20 to account for the fact that test subjects in the Nelson study were exposed to isopropanol for only 3-5 minutes. The combined effect of OEHHA's approach is to apply an uncertainty factor of 2000 to the mild eye, nose and throat irritation reported in Nelson. The Panel believes that this information suggests at most, an uncertainty factor of 10.

Response: OEHHA recognizes that the weakness of the isopropanol database requires the use of several uncertainty factors. However, no data were presented in the comment in support of using uncertainty factors other than 10 to account for sensitive individuals. The revised REL therefore includes an uncertainty factor of 10 to account for sensitive individuals.

Data sets from other chemicals with sensory irritant properties, such as chlorine and ammonia, indicate that the adjustment for duration of exposure is applicable to sensory irritants. Such an adjustment is not an uncertainty factor, but an exposure time adjustment for dosage. The precise time-concentration response relationship for isopropanol is unknown. Therefore, Haber's relationship, adjusted based on empirical data for other substances, was applied to account for the brief, 3-minute duration of the Nelson study protocol. The uncertainty factor for the revised REL is therefore 10 and the time-concentration adjustment is a factor of 20 to achieve a 1-hour concentration.

Comment: OEHHA should not group, under the category of "respiratory irritation", the eye, nose and throat irritation reportedly caused by isopropanol with other types of respiratory tract irritation that involve different mechanisms of action and severity of effect (e.g., pulmonary irritation).

Response: Most chemicals have multiple mechanisms of toxicity and target tissues, even though it may be possible to determine a single principal toxicological effect. One disadvantage of the Hazard Quotient approach is the potential for ignoring secondary effects or secondary target sites. Because of this, OEHHA has suggested designating the entire respiratory tract as a target organ, rather than speciating each cell and tissue type separately and delineating various regions of the lung as separate target sub-sites. To do otherwise may ignore data gaps and gray areas where chemicals affect both upper and lower tracts to varying degrees, in addition to possible systemic effects and influences. The result is a simplified approach, suitable for risk assessment, that does not assume exclusivity about the region of effect in the respiratory tract of a chemical simply because data gaps prevent a more precise estimation of the chemical's effects. Since the critical effects are given in each toxicological summary, it is possible for risk managers to sort out those cases in which contributions to a respiratory HQ greater than 1 are deemed to be restricted only to the upper airways from those when the only target site is known to be the lower airways.

Comment: OEHHA's conservative REL for isopropanol has practical negative consequences for industrial facilities, the public and regulatory agencies. The program will impose substantial costs on industrial facilities and local Air Quality Management Districts with little risk reduction benefit. In addition, this REL may have a negative impact on pollution prevention efforts by discouraging companies from using isopropanol, which has relatively low photochemical reactivity and toxicity. Companies may switch to more toxic chemicals with higher RELs. Finally, because OEHHA's REL for isopropanol is extremely low and inconsistent with other published values, the REL will produce unnecessary alarm in the workplace and communities, and will cause confusion about actual environmental risks.

Response: OEHHA is not recommending discontinuation of use for isopropanol; the REL has been reevaluated to reflect comments from the Panel. It is important to note that the critical limitation for the derivation of the REL for isopropanol is the lack of data. Additional studies on the toxic effects in a controlled human study would reduce the uncertainty in deriving an REL for this substance.

References:

American Conference of Governmental Industrial Hygienists (ACGIH). Documentation of Threshold Limit Values and Biological Exposure Indices. Cincinnati (OH): ACGIH; 1991.

Gill MW, Burleigh-Flayer HD, Strother DE, Masten LW, McKee RH, Tyler TR, Gardiner TH. Isopropanol: Acute vapor inhalation neurotoxicity study in rats. J Appl Toxicol 1995;15(2):77-84.

Ketones Panel

The main points in the comments were the following:

Comment: OEHHA's proposed one-hour reference exposure level (REL) for MEK is 4000 times lower than the American Council of Governmental Industrial Hygienists (ACGIH) 8-hour threshold limit values (TLV), 6000 times lower than the ACGIH 15 minute short-term exposure limit (STEL), 7 times lower than the EPA Integrated Risk Information System (IRIS) reference concentration (RfC), and 300 times lower than the odor threshold for MEK. As a result of these inconsistencies, the REL for MEK lacks scientific plausibility. For example, it is implausible to have an acute REL, above which the general population should not be exposed for more than one hour, that is seven times lower than the RfC, to which the general population may be exposed every day for a lifetime without adverse effect.

In addition, the proposed REL for MEK is approximately the same as the proposed REL for chlorine, even though Occupational Safety and Health Administration (OSHA) and ACGIH published values show that chlorine is at least 300 times more acutely toxic than MEK. These essentially identical RELs for compounds considered quite different toxicologically cast doubt on the validity of OEHHA's REL for MEK.

OEHHA should modify its derivation of the REL for MEK to ensure a scientifically plausible result. Specifically, the REL should be based on the more recent and more comprehensive study by Dick *et al*. (1992), not on Nelson *et al*. (1943). Even if the study by Nelson *et al*. is used, however, mild irritation should not be considered an adverse effect for regulatory purposes. As a result, 200 ppm should be considered a no observed adverse effect level (NOAEL).

OEHHA proposes to use an uncertainty factor of 10 to extrapolate from a LOAEL to a NOAEL; an uncertainty factor of 10 to protect the sensitive subpopulations; and a factor of 20 to account for the fact that the subjects in the Nelson study were exposed to MEK for only 3-5 minutes. The combined effect of OEHHA's approach is to apply a safety factor of 2000 to the mild eye, nose and throat irritation reported in Nelson.

Responses: OEHHA has reevaluated the REL for MEK based on the additional information received. A revision of the MEK acute toxicity summary includes a description of the Dick *et al*. (1992) study and the derivation of an REL based upon data reported by Nakaaki (1974). While it is apparent that the subjects in the Nakaaki study experienced mucous membrane irritation from MEK during exposure, the nature of the study does not allow for the standard determination of the NOAEL and LOAEL for irritation. However, it is clear that the subjects would experience mucous membrane irritation over a 2-hour period if exposed to the highest concentration of MEK achieved in the study. Given that the study by Dick *et al*. (1992) was inconclusive for irritation and that it was unclear from the Nakaaki study whether the lowest concentrations of MEK (starting at 90 ppm) resulted in anything other than odor perception, an uncertainty factor of 3 should provide an adequate margin of safety to arrive at the NOAEL. The REL therefore changed from 1.5×10^2 to 2.6×10^4 $\mu g/m^3$.

OEHHA maintains that mild sensory irritation is an adverse effect. This was also acknowledged by ACGIH (1991) and was the basis for the TLV for isopropyl alcohol.

Comment: The Panel believes that an uncertainty factor of two or three is sufficient to extrapolate from a LOAEL to a NOAEL for mild effects such as the irritation reported in the Nelson study. Moreover, an uncertainty factor of 2.5 is sufficient to protect sensitive subpopulations. No correction factor is needed to extrapolate from shorter duration studies to a one-hour value for chemicals such as MEK whose effects are not time-dependent. The Panel therefore believes that at most, OEHHA should apply an uncertainty factor of 10 to the LOAEL it identified in the Nelson study.

Response: The REL development methodology now specifies an uncertainty factor of 3 to extrapolate from a LOAEL to a NOAEL for mild sensory irritation. OEHHA is willing to consider the use of an uncertainty factor other than the default of 10 for the protection of sensitive individuals where data are available. In general, the range of human susceptibility to the effects of chemical exposure has been found to be greater than 3 fold (Hattis D. Variability in susceptibility-- how big, how often, for what responses to what agents? Environ Toxicol Pharmacol 1996;2:135-145; Horstman D, Roger LJ, Kehrl H, Hazucha M. Airway sensitivity of asthmatics to sulfur dioxide. Toxicol Indus Health 1986; 2:289-298). The adequacy of the default uncertainty factor of 10 is discussed in the response to Monsanto Company (#4-8).

Comment: OEHHA should not group, under a single category of "respiratory irritation," the eye, nose and throat irritation reportedly caused by MEK with other types of respiratory tract irritation that involve different mechanisms of action and severity of effect (e.g., pulmonary irritation).

Response: OEHHA disagrees with the comment that grouping respiratory effects by mechanism of action would be useful for the risk assessment process. Most chemicals have multiple mechanisms of toxicity. Additionally, multiple indirect influences on organ physiology cannot be disregarded simply because the molecular or cellular targets of two chemicals are not identical. For example, one chemical may influence the toxicity of another chemical by inducing metabolic enzymes or by decreasing intracellular glutathione, even though the "mechanism" of toxicity of the two chemicals may be quite different. In fact, when considering the full complexity of this issue, it must also be acknowledged that potentiation (supra-additivity) likely often occurs and is not accounted for. Adding a mechanism of action parameter to the risk assessment methodology would create an additional layer of complexity and would require many chemicals to be placed in an "unknown mechanism" category.

Comment: OEHHA's conservative RELs have practical negative consequences for industrial facilities, the public and regulatory agencies. The program will impose substantial costs on industrial facilities with little risk reduction benefit. In addition, this REL may have a negative impact on pollution prevention efforts by discouraging companies from using MEK, which has

relatively low photochemical reactivity and toxicity. Companies may switch to more toxic chemicals with higher RELs. Finally, because OEHHA's REL for MEK is extremely low and inconsistent with other published values, the REL will produce unnecessary alarm in the workplace and communities, and will cause confusion about actual environmental risks.

Response: The new REL for MEK based on Nakaaki (1974) is considerably higher than the previous REL. Although the study suggested by the panel was not the most appropriate study for the REL for MEK, OEHHA appreciates the positive contribution of the comments toward improving the REL for MEK.

References:

American Conference of Governmental Industrial Hygienists (ACGIH). Documentation of Threshold Limit Values and Biological Exposure Indices. Cincinnati (OH): ACGIH; 1991.

Dick RB, Krieg EF Jr, Setzer J, Taylor B. Neurobehavioral effects from acute exposure to methyl isobutyl ketone and methyl ethyl ketone. Fundam Appl Toxicol 1992;19:453-473.

Nelson KW, Ege JF, Ross M, Woodman LE, Silverman L. Sensory response to certain industrial solvent vapors. J Ind Hyg Toxicol 1943;25:282-285.

Schwetz BA, Leong BKJ, Gehring PJ. Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol. Appl. Pharmacol. 1974;28:452-464.

Methyl Bromide Panel

The main points in the comments were the following:

Comment: The proposed level II REL and toxicologic endpoint for methyl bromide are based on data that have been found to be inconclusive.

OEHHA's draft guidelines would establish a Level II REL of 1 ppm (3.9 mg/m^3) and a "reproductive-developmental" toxicologic endpoint for methyl bromide. The REL apparently is based on one study, which is identified as Breslin, W.J. *et al*, 1990. The Methyl bromide Inhalation Teratology Study in New Zealand White rabbits, Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company Midland, MI, Study No. K-000681-033. ("Breslin Study"). This study purported to establish a six-hour no observable effect level (NOAEL) of 40 ppm. OEHHA applied an uncertainty factor of 100 to this NOAEL to generate the proposed one-hour LEVEL II REL for methyl bromide.

The proposed "developmental-reproductive" toxicologic endpoint for methyl bromide appears to be based on the Breslin Study and two additional studies: 1) Sikov *et al*. 1981. Teratologic Assessment of Butylene Oxide, Styrene Oxide, and Methyl Bromide. NIOSH Technical Report, Publication no. 81-124, U. S. GPO (Sikov Study); and 2) Hardin, *et al* . 1981 . Testing of Selected Workplace Chemicals for Teratogenic Potential, Scand. J. Work Environ. Health 4:66-75 (Hardin Study) . As more fully explained below, the use of the Breslin Study to calculate the REL, and of all three identified studies as the basis for a "developmental-reproductive" endpoint designation, is inappropriate.

First, all three studies have been found to be scientifically insufficient to support the conclusion that methyl bromide produces developmental toxicity. In 1994, these studies were specifically evaluated by the California Developmental and Reproductive Toxicity Committee (DART) and determined to present inconclusive evidence of developmental or reproductive effects. Thus, they could not be used as the basis for designating methyl bromide as a developmental or reproductive toxicant under the Birth Defects Prevention Act (Proposition 65).

Response: OEHHA has acknowledged the findings of the DART committee regarding the Breslin *et al*. (1990) study. Although there was insufficient evidence for the DART committee to classify MeBr as a reproductive toxicant, MeBr still causes serious adverse health effects in animals in the above studies. We have developed a value for MeBr protective of those adverse effects, but are not designating the substance as a reproductive toxicant. The California Proposition 65 qualified listing of MeBr was that of a reproductive toxicant when used as a structural fumigant. The DART committee ruling that insufficient evidence existed to consider methyl bromide a developmental or reproductive toxicant for the purposes of a full Proposition 65 listing does not necessarily invalidate the developmental defects in the Breslin *et al*. (1990) study, or the maternal CNS effects seen in the Breslin *et al*., Hardin *et al*. (1981), or Sikov *et al*. (1981), studies. Similarly, this ruling does not necessarily contradict the assessments by USEPA or the California Department of Pesticide Regulation, both of which consider methyl bromide a reproductive/developmental toxicant.

Comment: The Sikov Study was deemed inconclusive because the effects were considered by the authors to be of questionable biological significance. The Hardin Study was deemed inconclusive due to maternal toxicity, and the Breslin Study was found to be inconclusive because of the nature of the effects shown, and the presence of severe maternal toxicity that likely contributed to several effects purportedly observed in the offspring.

In light of the Committee's findings with respect to the Breslin Study, the 40 ppm NOAEL purportedly established by this study is unreliable because it is based on equivocal effects. Thus, it should not be used as the basis for OEHHA's calculation of an REL for methyl bromide.

Response: The adverse effects of methyl bromide on the test species in the above studies were significant. It is unclear if the studies have a sufficient basis to consider the compound a reproductive toxicant for humans. The REL developed is intended to protect against all serious adverse effects, including those classified as maternal toxicity. The issue of developmental defects being secondary to maternal toxicity is therefore immaterial for the purposes of a severe adverse effect level for methyl bromide, since both the maternal CNS effects and the adverse developmental outcomes are serious (severe adverse effect level effects). The comment acknowledges the severe maternal toxicity seen in each of these studies. The maternal effects in these studies (including weight loss, CNS disturbances, and death) were not equivocal, and should be considered serious by any standard. For this reason, they formed the basis of the REL developed.

Comment: OEHHA's designation of a "developmental/reproductive" toxicologic endpoint for methyl bromide also is unjustified in light of the inconclusive nature of all three studies. The Technical Support Document acknowledges the DART Committee's conclusion that these studies are insufficient to support a determination that methyl bromide is a developmental toxicant yet, despite this acknowledgment, OEHHA nonetheless concluded that it was appropriate to designate a "developmental-reproductive" endpoint for methyl bromide. Absent a complete re-evaluation of all three studies, this is in direct conflict with the scientific judgment of the DART Committee, as well as numerous experts in the field of developmental toxicity that evaluated these studies in the context of the Committee's deliberations.

Response: The criteria for listing a chemical by the DART committee as "known to the State to cause reproductive toxicity" require that it clearly be shown that the chemical causes such toxicity. The DART committee concluded that this strict standard was not met for methyl bromide. However, other agencies, such as USEPA and the California Department of Pesticide Regulation concluded from an extensive evaluation of all the above studies that methyl bromide caused developmental/reproductive effects in rabbits and rats, as discussed above.

Comment: An extensive acute inhalation toxicology database exists for methyl bromide which provides data consistent with OEHHA's underlying intent in determining acute one-hour REL

values. Thus, as more fully explained below, the MBIP believes that OEHHA should revise its endpoint designation and recalculate the REL using data that has greater scientific validity.

Response: The acute inhalation toxicity database for sub-lethal effects of methyl bromide is not extensive. The only sub-lethal acute inhalation toxicity data come from unpublished reports and studies with a small sample size. Virtually no epidemiological information has been reported regarding acute inhalation of methyl bromide and reproductive or developmental toxicity in workers.

Comment: The methodology underlying OEHHA's REL for methyl bromide is scientifically flawed because it uses data derived from a repeated-dose study.

In addition to the foregoing, OEHHA's use of the Breslin Study is inappropriate for other reasons. The Breslin study is a repeated-dose study. As more fully explained below, the use of such studies to calculate a one-hour Level II REL is scientifically unsound for chemicals such as methyl bromide because the toxicologic profile from acute exposure to methyl bromide is different from that produced by repeated exposures.

The MBIP understands that OEHHA's extrapolation from six-hour exposure data to an acute one-hour REL is based on an application of Haber's law. As a matter of scientific validity, Haber's law may be suitable for determination of an acute one-hour REL by extrapolation from 6-hour acute exposures. However, the use of Haber's law with assigned magnitude factors to extrapolate a one-hour REL from repeated-dose studies is not justified for risk estimation purposes, especially for chemicals such as methyl bromide.

Studies conducted with methyl bromide in several animal species, using both single and repeated-dose exposures, clearly show a steep dose response curve. Repeated-dose studies with methyl bromide demonstrate that the toxicological effects seen in those studies are different from those seen in acute studies. Animals can tolerate acute exposure at high concentrations without effect, whereas repeated exposures at lower concentrations may produce serious toxicity.

For example, in a study conducted at the request of the California Department of Pesticide Regulation (CDPR), daily repeated exposure (7 hours/day) to a methyl bromide concentration of 150 ppm (127 mg/kg/day dose equivalent) produced severe neurologic deficits and abnormality after 5 or 6 exposures. After 1 or 2 exposures at 150 ppm, the dogs were generally asymptomatic. Similarly, a single 7-hour exposure to a methyl bromide vapor concentration of 233 ppm was considered a NOEL. When dogs were exposed to 100 ppm (85 mg/kg/day dose equivalent) on a 7 hour per day, 5 day per week regimen for 4 weeks, no neurological effects nor mortality were seen. These results clearly demonstrate that the toxicologic profile from an acute exposure to methyl bromide is different from repeated exposure. These differences are directly pertinent to the developmental toxicity data used by OEHHA in its calculations. Developmental toxicity studies are repeat-exposure studies. In typical studies, pregnant females are exposed for 10 to 15 consecutive days during gestation. It is well documented in the literature that developmental toxicants produce effects at specific critical times during fetal development and

that the effects are chemical specific. Repeated doses are necessary to assure that a sufficient dose occurs during the critical developmental stages.

Response: The presentation of the results of the dog study are in error. As a result of the errors (explained below) the conclusion regarding single and repeated exposures can be made from this study. First, the NOAEL for the 7-hour Pharmaco-LSR study was not 233 ppm as stated in the comment. At this concentration, dogs were observed to be trembling, panting and blinking rapidly during exposure. Second, the comment that no neurological effects were seen following exposure to 100 ppm is also incorrect. At 100 ppm, dogs showed neurological signs (decreased activity, tremors, and emesis) and decreased body weight gain.

OEHHA acknowledges that the time-extrapolation from multiple exposures to a 1-hour exposure is not ideal. However, as indicated in the comment, for a number of substances tested in developmental toxicity research it has been shown that exposure to a dose of chemical during a critical period of development can result in adverse development of the fetus (e.g., in the case of thalidomide). Thus, unless information to the contrary is available for the chemical in question, it is prudent to assume that a single exposure to a teratogen may result in adverse developmental outcome. Since this is the case and since virtually all available reproductive/developmental studies are repeated exposure studies (as pointed out by the comment), a single daily dosage is therefore thought to be sufficient for the occurrence of developmental toxicity. In the case of methyl bromide, the comment may be correct that there appears to be a pattern for cumulative neurotoxicity. The mechanism for this cumulative neurotoxicity is not known. A thorough evaluation of the Pharmaco-LSR data by staff from both DPR and OEHHA indicated that 103 ppm was the highest acute NOAEL in the multi-day study. One dog exposed to the next higher concentration (156 ppm) experienced lacrimation after 5 hours exposure. After 3 days exposure to 156 ppm, dogs showed significant neurological effects.

External peer reviewers, chosen by OEHHA and DPR, of the Pharmaco-LSR data concluded that time-extrapolation was not feasible due to the poor quality of the data in terms of sample sizes and number of independent dose-groups. Therefore, OEHHA proposes to use the 103 ppm value as an appropriate NOAEL for the purposes of determining an acute standard. Inclusion of a standard margin of safety of 100 results in an acute REL of 1 ppm.

Comment: A single acute dose of a developmental toxicant would not be effective unless the fetus were in the specific affected period of development and the appropriate dose were used. Thus, the use of results from repeated-dose developmental studies as an endpoint for extrapolation to a one-hour REL constitutes an “apples to oranges” assessment. In light of the nature of repeated-dose developmental toxicity studies, the extrapolation should be based on a “precise moment in time” effect rather than discrete measurable endpoints (such as neurotoxicity, death, etc.) noted in acute toxicity studies.

Response: The repeated dose studies resulted in neurotoxicity. The neurotoxic effect of methyl bromide is not well understood. The extrapolation from repeated exposure experiments to a 1-hour exposure is more accurate when bioaccumulation of the chemical or a cumulative effect

upon the animal is not present. However, with methyl bromide, serious neurological effects are seen after a small number of successive acute episodes in most animals, even though a one-time exposure does not reveal these effects. The dose-response slope is clearly very steep in this case and the mechanism for the cumulative effect is not known. The adequacy of a REL based on a 1-hour exposure would therefore be dependent upon any prior exposures to methyl bromide. In practice, the risk assessments for the Air Toxics Hot Spots program look at one-hour maximum exposures to compare to the REL. This one hour maximum may occur concomitantly to other high one-hour exposures slightly below the REL. Methyl bromide is emitted from Hot Spots facilities. It is entirely plausible that several one-hour periods of relatively high exposure occur since meteorological conditions drive the exposures. Repeat exposures are quite likely for communities near sources of methyl bromide.

The single, acute exposure from the Pharmaco-LSR study in dogs is now proposed as the new basis for the REL.

Comment: For these reasons, the MBIP believes that OEHHA should consider other approaches to determining the one-hour REL for methyl bromide. An appropriate calculation of the REL is provided below.

The proposed level II REL should be recalculated using data from the extensive acute inhalation toxicity database available for methyl bromide.

The MBIP believes that the REL should be recalculated using data from the extensive acute inhalation toxicology database that exists for methyl bromide. For the reasons outlined above, the extrapolation of an acute one-hour REL from an acute 6-hour exposure is considered an appropriate approach because similar toxic endpoints are assessed.

Using the results from the acute, single, 7-hour inhalation exposure in dogs described above, a methyl bromide vapor concentration of 230 ppm was the No Observable Effect Concentration (NOEC). This methyl bromide concentration provides a total exposure dose of approximately 195 mg methyl bromide/kg body weight/day (mg/kg-d) using respiratory minute volume and standard body weight values (Biology Data Book, Vol 3 74).

This animal dose permits the calculation of a human equivalent exposure concentration as follows:

195 mg/kg-d x 24.45/94.95 x 1/0.046 m^3/kg-day = 1091 ppm

*human minute volume = 7.43 1/min
human body weight = 68.5 kg
human exposure 7 hours

As a standard practice (also used by OEHHA in calculating RELs), a 100-fold factor is used to assess human safety when extrapolating from animal doses to man. On this basis, a concentration of 10.91 ppm (1091 ppm/100) would be considered as an acceptable exposure concentration for

man over a 7 hour period. Using a similar approach to the DOT Criteria above for vapor exposure (2 x the 4-hour LC_{50}), a 1-hour REL can be calculated as follows:

Adjusted NOEC	(7 hours/2)	=	l-hour REL
1.91 ppm	x	3.5	= 38.2 ppm

The MBIP urges OEHHA to recalculate the REL for methyl bromide using like data for comparative assessments. In order to calculate an acute 1-hour REL, OEHHA should utilize results from other acute inhalation tests. As noted above, extensive acute inhalation toxicity data are available for such purposes. Using the results from the MBIP's recent acute inhalation exposure study in dogs, a l-hour REL of 38.2 ppm would be considered appropriate for methyl bromide. The MBIP appreciates the opportunity to comment on OEHHA's draft risk assessment guidelines and the proposed REL for methyl bromide. For all the reasons discussed above, the MBIP urges OEHHA to revise its toxicologic endpoint designation, and recalculate the REL using data from the extensive acute inhalation toxicity database that exists for methyl bromide. A more appropriate calculation would result in a one-hour Level II REL of 38.2 ppm.

Response: Using the data from the above report, OEHHA has recalculated the REL for methyl bromide based on severe CNS effects following acute inhalation exposures in dogs. The methodology presented in the comment (e.g., use of DOT methods to account for duration of exposure and use of default breathing rates) is not appropriate for, or consistent with OEHHA's Guidelines for the Determination of Acute Toxicity Exposure Levels. Furthermore, an independent scientific review of the data from the dog study concluded that time-extrapolation should be avoided for the purposes of determining an acute REL. Default breathing rates are often not appropriate since we are concerned about child breathing rates, not averaged over a day or a lifetime, but which might occur when a child is outside at play. Finally, as discussed at length above, 230 ppm is not an appropriate NOAEC for the start of the calculation. For these reasons, the recalculated severe adverse effect level for methyl bromide is 1 ppm, not 38.2 ppm. OEHHA found the comments useful in contributing to the REL generation process. We have worked with toxicologists from the Department of Pesticide Regulation and recalculated the REL based on the newer data presented while being consistent with independent scientific reviewer recommendations to avoid time-extrapolation when using these data. As a result, the recommended 1-hour acute REL remains at 1 ppm.

Phenol Task Group

The Task Group's main comments were the following:

Comment: The Task Group urges OEHHA to revise its risk assessment methodology so that it does not yield overly conservative values.

Response: The methodology proposed by OEHHA includes some uncertainty factors to match the data gaps which are ubiquitous in the toxicological literature. When these data gaps have been reduced, the magnitude of the uncertainty factors used for specific chemicals have likewise been reduced. This can be seen in the benchmark dose calculations, and in many chemicals where adequate human data exist to characterize practical thresholds for sensitive individuals. The uncertainty factors in all these cases were reduced. In this way, the methodology proposed by OEHHA is responsive to the best scientific information, while safeguarding public health when significant uncertainties exist.

Comment: Even if OEHHA does not revise its risk assessment methodology, the Task Group urges OEHHA to maintain the proposed Level II and Level III values, which are identical to the AIHA ERPG-2 and ERPG-3 values, respectively.

Response: The AIHA (1992) ERPG-2 and ERPG-3 for phenol were recommended for reevaluation due to serious errors in the ERPG documentation. The critical concerns with the ERPG values for phenol are discussed below.

As the basis of the ERPG-2, Flickinger *et al*. (1976) was incorrectly cited as reporting a 1-hour exposure to 312 ppm in rats resulting only in lacrimation. The actual study reports that slight loss of coordination, in addition to signs of ocular and nasal irritation, was observed after 4 hours of exposure to 235 ppm. The second key reference for the ERPG-2 is an occupational report (ACGIH, 1984) of eye, nose, and throat irritation in workers intermittently exposed to 48 ppm phenol and 8 ppm formaldehyde; the eye irritation was considered to be caused by the formaldehyde. However, the ERPG document cites an irritation threshold of 47 ppm for phenol (Ruth, 1986). This latter finding suggests that the occupational exposure of 48 ppm phenol actually represents a LOAEL and should be treated accordingly.

The ERPG-3 was recommended for reevaluation because the basis for this level was slight loss of coordination and signs of ocular and nasal irritation observed in rats following a 4-hour exposure to 235 ppm phenol. The endpoints used are not appropriate for the development of a life-threatening effect level. As identified in Table 5 of the Technical Support Document for the Determination of Acute Toxicity Exposure Levels for Airborne Toxicants, appropriate effects on which to develop a value for the life-threatening effects level include severe pulmonary edema, respiratory arrest, ventricular arrhythmia, cardiac arrest, and death. Therefore, as more appropriate data become available, it is the intent of OEHHA to revise the existing severe adverse effect level and life threatening effect level currently based upon the ERPG-2 and ERPG-3, respectively.

Comment: The Task Group urges OEHHA to revise upward the proposed Level I (REL) value of 0.038 ppm, which the Task Group believes is overly conservative and not appropriate for the purposes stated. The Task group urges OEHHA not to use a 100-fold uncertainty factor for establishing the phenol Level I (REL) value.

Response: In response to this comment, OEHHA has revised the REL for phenol, based on the Piotrowski (1971) human data. The REL has changed from 1.5×10^2 to 5.8×10^3 µg/m³.

Comment: The Task Group urges OEHHA to consider existing standards for phenol, which are orders of magnitude different from the proposed Level I (REL) value. Most relevant here is the AIHA "ERPG-1" value for phenol of 10 ppm.

Response: The ERPG-1 was developed for rare accidental chemical releases and not the routine exposures that are being evaluated under the Hot Spots program. Thus, ERPGs are not appropriate values for RELs. Nonetheless, the ERPG-1 was evaluated by OEHHA.

The ERPG-1 is based upon a free-standing acute NOAEL in humans and upon a free-standing chronic NOAEL in rodents. Of greatest concern to OEHHA was that the ERPG-1 was set approximately two-fold higher than the reported NOAELs without explanation. While OEHHA is not averse to using the human free-standing NOAEL reported, it is not appropriate to use chronic animal data without consideration of interspecies and exposure duration differences, as is done in the ERPG-1.

As explained above, the REL for phenol has been reevaluated using the Piotrowski (1971) human study.

Comment: The Task Group urges OEHHA to revise its discussion of phenol toxicity data to describe more fully the existing data.

Response: OEHHA has reviewed its description of the key studies in question and has supplemented the descriptions accordingly to reflect comments received. For example, the chronic toxicity data presented by Sandage (1961) was previously reviewed by OEHHA and was omitted from the acute toxicity summary for phenol because the data do not characterize responses to acute exposure. However, the revision of the acute toxicity summary will include a description of this chronic animal toxicity data. Also, the description of the Deichmann (1944) inhalation toxicity study has been rewritten to emphasize the rat data in order to reflect comments that, of the species tested, rat metabolism of phenol is closest to that of humans.

References:

American Conference of Governmental Industrial Hygienists (ACGIH). Documentation of Threshold Limit Values and Biological Exposure Indices. Cincinnati (OH): ACGIH; 1984.

American Industrial Hygiene Association (AIHA). Emergency Response Planning Guidelines. Akron (OH): AIHA; 1992.

Flickinger CW. The benzenediols: catechol, resorcinol and hydroquinone-a review of the industrial toxicology and current industrial exposure limits. Am Ind Hyg Assoc J 1976;37:596-606.

Piotrowski JK. Evaluation of exposure to phenol: absorption of phenol vapor in the lungs and through the skin and excretion of phenol in the urine. Br J Ind Med 1971;28:172-178.

Ruth JH. Odor thresholds and irritation levels of several chemical substances: a review. Am J Ind Hyg Assoc J 1986;47:A142-A151.

Sandage C. Tolerance criteria for continuous inhalation exposure to toxic material. I. Effects on animals of 90-day exposure to phenol, CCl_4, and a mixture of indole, skatole, H_2S, and methylmercaptan (ASD Technical Report 61-519). Wright Patterson Air Force Base (OH): US Air Force Systems Command, Aeronautical Systems Division; 1961. Available from NTIS, Springfield, VA. NTIS # AD-268783.

Citizens for a Better Environment

The comment contains two specific concerns:

Comment: Add MTBE to the list of chemicals for evaluation since it is widely used in refineries and for reformulated fuels. The chemical was banned in Alaska because of associated acute health problems.

Response: The health impacts of MTBE have generated concern relatively recently. OEHHA agrees with the comment that acute exposure values protective of public health from MTBE should be developed. Although it is not possible for an addition to the present document, we are working with the Air Resources Board to prioritize substances for future evaluation. Data are not available for OEHHA to develop an acute REL for MTBE at this time.

Comment: Add all chemicals which have been released by Bay Area refineries and chemical plants during the chemical accidents of the last 10 years. Petrochemical facilities have had a poor safety record in recent years, and have been a major source of community acute exposure to chemicals.

Response: The chemicals on the current list include those identified as chemicals of concern by the California Air Pollution Control Officers Association (CAPCOA) in 1993 and many additional compounds that are released in large quantities by facilities in the State. The focus of the document is on predictable controlled releases, rather than on spills or accidental releases. There are still many chemicals that require toxicological evaluation and subsequent health value development, and OEHHA is committed to completing this work as soon as possible. OEHHA will continue to add chemicals to the list based on the needs of local agencies and risk managers, in addition to those chemicals released in high volume.

City Of Los Angeles, Bureau of Sanitation

GENERAL COMMENTS

Deterministic versus Probabilistic Models

Comment: Risk assessment criteria and procedure development are under critical review by many organizations at this time. The major criticism has been that deterministic assessments are too subjective and limiting in their scope and do not objectively consider the possibility of deviations from fixed values. The Bureau agrees that deterministic models are too limiting and do not accurately measure potential acute health risk, therefore we strongly recommend that the probabilistic health risk exposure model be used.

We believe that the use of models must be accompanied by a recognition of their inherent limitations and a knowledge of the uncertainties associated with model input and outputs. Models should not be viewed as "black boxes" that yield a single absolute value, but rather must be accompanied by good judgment and knowledge of their role as part of a suite of tools available for policy analysis and decision-making. New and improved tools are needed to assist policy-makers with decisions so that equitable and effective emissions management practices can be applied.

The discussion and analysis presented in Part I and in the Technical Support Document clearly demonstrate that risk/exposure assessment must incorporate a large amount of uncertainty into the evaluation. For example, the uncertainty and modifying factors utilized to determine effective models add additional levels of subjectivity to the values used in deterministic models. As a result of this uncertainty, we question the value of comparing a point value for the estimated exposure/risk to a point value for acceptable exposure/risk as done in the "bright line test". Probabilistic modeling method uses all of the information available about the variability and uncertainty inherent in the assessment, while deterministic assessments discard most of this type of information. Probability distributions thus present the range of exposures or risks not available using deterministic methods.

Response: OEHHA agrees with the comment that probabilistic models are valuable tools when it is possible to use them. The use of distributions to characterize ranges of risk requires adequate data and is therefore more appropriate for assessment of exposure than for determination of toxicological thresholds. For example, for nearly all chemicals, the precise toxicological response distributions of individual thresholds are simply not known, even in laboratory animals. Furthermore, although some specific areas of interspecies differences (metabolism, toxicodynamics, etc.) may be addressed to varying degrees in the literature, it is extremely rare to have enough data to adequately characterize interspecies uncertainty. Uncertainty factors, though somewhat subjective, are used to account for real areas of uncertainty and variability. A considerable body of literature shows that many of the traditional uncertainty factors accurately account for certain areas of variability. For example, the report submitted by Monsanto Company using data from the World Health Organization and other sources (see attached) shows that an uncertainty factor of 10 adequately accounts for interspecies differences in most cases. These

factors are therefore not merely artifacts of risk management decisions. Unless considerable data exist to support a range for each chemical, the uncertainty factor method should be used. Recent analyses presented at the Society of Toxicology meetings in 1997 reported that probabilistic analyses are generally consistent with the uncertainty factor approach. Probabilistic methodologies are part of the Hot Spots Technical Support Document for Exposure Assessment and Stochastic Analysis, which is a separate document under review.

SPECIFIC COMMENTS

1) Interpretation and Definition of an Acute HI

Comment: A bright line test is not necessarily the best way to present risk/exposure information for another reason. A well defined threshold value should generate a factor that clearly alerts the impacted population that concern is warranted. If the public does not perceive any hazard then a credibility gap could form, and the hazard index may be widely disregarded.

Response: The reference exposure level (REL) is the level at or below which adverse health impacts are not expected for the majority of the population. When exposure concentrations exceed the REL, there exists a gray area where one cannot predict with certainty when adverse impacts will be manifested until a concentration that produces frank or severe effects is reached. RELs are based on the best available scientific data for each compound. The data simply are non-existent to characterize the distributions of individual toxicologic thresholds for each chemical and endpoint. Uncertainty factors are used in many cases since detailed dose-response data in sensitive individuals do not exist. As the comment has pointed out, the onset of toxicant-induced symptoms in the population is probabilistic, and follows a distribution. The purpose of the RELs is to account for those responses at the sensitive tail-end of that distribution. Generating RELs at which large numbers of people reported adverse health impacts would be inappropriate.

The bright line test is a risk management decision and, while it has its limitations, it currently is one way a risk manager can feel certain about protecting public health. Whether the public perceives a hazard is an issue unrelated to setting science-based health-protective RELs.

Comment: The proposed system to determine RELs has been highly diluted with modifying and uncertainty factors such that the hazard indices generated under this system generally do not represent any real acute health threat to the exposed population. The guidelines for the evaluation of the acute impacts, while based on the sound toxicological data, are adjusted to reflect the risk to only the most sensitive portions of the population. Ten of the 53 compounds listed in the document, with reference exposure levels, are flagged as compounds with Level II effects. Level II compounds are those which may cause exposed individuals to seek assistance after an exposure period of 1 hour. One of these ten compounds is perchloroethylene used in the dry cleaning industry. The REL given is more than an order of magnitude less than either the odor threshold and any industrial worker standard.

Customers often observe workers in dry cleaning facilities exposed daily to this "not unpleasant" smelling chemical at very perceptible concentrations and consumers will often smell the perchloroethylene off-gas from freshly cleaned clothing for most of [the] first day after cleaning. By definition, both are thus exposed to an acutely hazardous concentration. This situation establishes a very large credibility gap with the public regarding the hazard associated with (and other) compounds. This is not meant to indicate that there is not a real health threat from exposure to this compound, but we think that exposure at this very low REL should not be used to determine an acute HI. The public may be confused and may be skeptical as to the interpretation of an acute hazard.

Response: For purposes of clarification, OEHHA has defined acute reference exposure levels by duration of exposure (i.e., short-term, 1-hour exposures). The term acute may be used for different purposes in a medical context, and may sometimes imply a severity of the effect (e.g., the term "acute" can describe a short, sharp course). In the TSD, severity of effect is treated separately. It appears that this discrepancy in definitions may have created some confusion in the comment in the above statement.

It is true that the acute REL for perchloroethylene is lower than the occupational standards. However, there are two important issues that determine the REL for this compound. First, the adverse CNS effects used as the basis for the acute REL are from human data, with a specific, clinically significant change in a neurological test. There is, therefore, little uncertainty in the validity of the toxicological endpoint. The principal uncertainty lies in the small sample size of 3; thus an uncertainty factor of 10 was applied to account for sensitive individuals. Since no NOAEL was reported, an uncertainty factor of 10 was used to estimate a NOAEL from the LOAEL. Second, the occupational standard (50 ppm TLV) is based on prevention of irritation, not on neurological effects and includes only a 2-fold margin of safety. The ACGIH short-term exposure limit for perchloroethylene of 200 ppm is based on minimizing anesthetic effects, yet the LOAEL for CNS effects (impaired balance) in Stewart *et al*. (1970) was 100 ppm for 3 hours. These CNS effects are serious enough to potentially interfere with ability to escape exposure. Furthermore, the odor threshold for perchloroethylene is relatively high (2 - 71 ppm; AIHA, 1989), and is in the same range as the observed CNS effects. The fact that consumers and workers are exposed above the odor threshold does not mean that perchloroethylene is non-toxic at those concentrations.

2) Determination of Interim RELs

Comment: It is unreasonable to place the burden of determining interim RELs on the risk assessor for those compounds that OEHHA's toxicologists do not have enough data. OEHHA has the expertise and resources to develop RELs, however, most risk assessors just do not have the background in toxicology that OEHHA staff have. This action will completely subvert the acute HI assessment process as the focus will shift from the facilities' HI to the subjectivity and potentially self-serving REL. We recommend compounds with RELs developed by OEHHA be considered in the health risk assessment process.

Response: OEHHA recognizes the need for consistency and its unique responsibility in this area and has withdrawn this suggestion from the guideline.

3) Inclusion of Background Concentrations of Criteria Pollutants

Comment: The requirement that the background concentration of criteria pollutants should be included in the acute HI evaluation when the HI is greater than 0.5 is tantamount to establishing an acute HI notification level of 0.5 for almost all of the sources regulated by the SCAQMD. The risk/exposure assessment should reflect only the incremental increase as a result of the facility emissions.

Response: The acute REL document no longer includes the procedure of adding the criteria air pollutant effects to those of the non-criteria air pollutants.

4) Guidelines for Evaluation of Acute Risk

Comment: The guidelines for conducting the risk characterization (Section VII.D) are vague and do not comprehensively explain the procedures for evaluation [of] the acute risk. However, experience indicates that a precise risk characterization will represent a substantial amount of work. A number of computer dispersion model runs would be necessary in order to first locate the maximum exposed individual (MEI) resident, worker, and sensitive receptor to the total HI and then to determine the HI at the MEIs by organ or system for both level I and level II compounds. There are a number of approaches a risk assessor could take to complete this evaluation. OEHHA needs to develop detailed guidelines to assure the required data is presented in the risk assessment and that the approaches used by the risk assessors are consistent otherwise the results will not be comparable. These detailed guidelines need to be completed before Part - I guidelines are approved.

Response: OEHHA's draft exposure guidelines, titled "Exposure Assessment and Stochastic Analysis", was released for public comment in December, 1996. The dispersion modeling runs required to analyze the one-hour maximum are currently used for Hot Spots risk assessments.

Reference:

Stewart RD, Baretta ED, Dodd HC, Torkelson TR. Experimental human exposure to tetrachloroethylene. Arch Environ Health 1970;20:224-229.

The Clorox Company

Comment: Requiring action at a hazard index level of less than 1.0 in the risk assessment without safeguards to ensure that risk management identifies a hazard index action level of 1.0 or greater is poor policy.

Response: The acute REL document no longer suggests a specific HI.

Comment: Background pollutant concentrations should be compared to facility emissions, not added to them.

Response: The acute REL document no longer includes the previous procedure of adding the criteria air pollutant effects to those of the non-criteria air pollutants.

Harding Lawson Associates

There are four main categories of concern to the regulatory community; the first three address some sources of scientific uncertainty in OEHHA's approach, the fourth involves administrative aspects of finalizing and implementing the RELs. These concerns are:

Comment: *Lack of Precise Definitions for Toxicological Endpoints for Deriving Acute Exposure Levels*. OEHHA's definition and descriptions of RELs and acute exposure limits are presented in three statements in the Draft Technical Support Document:

1. Exposure Level I is "The discomfort or mild effect level...the concentration at or below which exposure for one hour may result in some odors, tastes and visual cues but which will cause no adverse health effects in nearly all of the population... Exposure at or below this level may be perceived by mild irritation of the eyes, nose or throat, or by unpleasant odors, tastes or sight" (OEHHA, 1995, page 11).

2. The REL, however, is defined as "the concentration level at or below which no adverse health effects are anticipated...RELs are based on the most sensitive adverse health effect reported in the medical and toxicological literature. As with acute toxicity exposure levels in general, RELs are designed to protect the most sensitive individuals in the population by the inclusion of margins of safety." (OEHHA, 1995, page 6).

3. OEHHA further states that "For chemicals with three acute toxicity exposure levels, Level I is considered the REL; for chemicals for which Level I is not appropriate (i.e., does not exist), Level II is the REL." (OEHHA, 1995, page 6).

These definitions are contradictory and not consistently applied in the derivation of acute exposure levels for individual chemicals. Based on the first definition, one would expect that mild or "discomfort" effects might occur at a Level I. By the second definition, adverse effects would not be expected to occur at an REL due to application of margins of safety; yet the third statement indicates that a Level I (or in some cases a Level II) is the same as an REL. Also, "adverse effect" and "adverse health effect" are not clearly defined. Unpleasant odors or visual appearances may be considered "adverse" or "undesirable", but they are not "adverse health effects" in any toxicological sense.

It is not clear whether or not the REL is to protect against all effects, however mild. Is the REL the mild effect level or the NOEL of the mild effect level (not NOAEL, as this effect is not considered an adverse health effect by OEHHA's definition)? Is a margin of safety for sensitive subpopulations to be applied to the mild effect level or the NOEL of the mild effect level? These definitions and procedures need to be clarified so that the basis of derivation of acute exposure limits for individual chemicals are clearly understandable to regulators, the regulated community and the interested public.

Response: The first quote taken from the OEHHA draft Technical Support Document: "***Exposure at or below this level may be perceived by mild irritation of the eyes, nose or throat,***

or by unpleasant odors, tastes or sight" is an error in the Document that has been corrected. The definition of Level I is as stated in the comment's second quotation from page 6: ***"the concentration level at or below which no adverse health effects are anticipated...RELs are based on the most sensitive adverse health effect reported in the medical and toxicological literature. As with acute toxicity exposure levels in general, RELs are designed to protect the most sensitive individuals in the population by the inclusion of margins of safety."***.

This correction addresses both concerns in the above comment. The methodological descriptions have been revised for clarity. OEHHA appreciates the reviewer's comment in pointing out the need to clarify the definitions.

Comment: *Limited Consideration of Toxicological Data.* Many of the RELs are based on a single study or a limited subset of relevant studies. However, consideration of all relevant data provides the most rigorous database for the development of human toxicity criteria (NRC, 1993). NRC guidelines (NRC, 1993) explicitly include a review of the overall toxicity database as a key step in the development of community exposure levels. In contrast, OEHHA indicates that literature searches have been completed for less than one-half of the chemicals for which acute exposure limits have been derived; that is, for the majority of the chemicals for which a REL is being released, the first step of reviewing the full extent of the relevant literature has not even begun. An incomplete data review at the outset of the development of exposure levels introduces unnecessary uncertainty into the process, and excludes the ability to estimate the magnitude of uncertainty in the value which has been developed.

Response: OEHHA agrees that full consideration of all relevant toxicological literature is vital to the risk assessment process. Consequently, OEHHA considered all available data for each of the RELs presented. Literature searches were conducted by OEHHA for all chemicals that have acute RELs. Since the release of this document, all literature searches contracted for have been completed. Furthermore, OEHHA added to the literature searches already provided by the occupational and other sources supported by the comment (NIOSH-IDLH, AIHA-ERPG, and ACGIH-TLV) and added these into the reference database of each chemical. References irrelevant to the acute inhalation non-cancer health effects for each chemical are not included in the bibliography for the sake of brevity. This information has been clarified in the revised document.

Comment: Page 3 of the draft document lists the various existing exposure guidelines reviewed by OEHHA. We noted that IDLHs were the only occupational exposure regulations and guidelines listed. There is a wealth of information on the acute effects of airborne contaminants in occupationally exposed workers that often gets overlooked in the derivation of community exposure limits and emergency response guidance for the general public. This information is contained in the documentation for the occupational exposure limits, and should be one of the first sources considered in a literature review.

Response: As stated above, OEHHA surveyed this literature in creating the RELs. Refer to Section 1.8 in the technical support document for a complete list of existing exposure guidelines reviewed by OEHHA.

Comment: We acknowledge that occupational exposure limits may not, by themselves, be appropriate for use in developing exposure Levels for general public, especially for chronic, continuous exposures. However, they may be justifiable to consider in developing acute exposure limits. As the acute exposure levels may be used as guidance in emergency response situations, the levels must be low enough to be protective, but must also "be high enough to minimize false alarms and over-response" (NRC, 1993). At the very least, occupational exposure limits may serve as a "reality check" against acute toxicity exposure levels developed by extrapolation from animal studies. Although there may be exceptions, a derived one-hour acute Exposure Level II for the general population may be overly conservative if it is lower than an occupational exposure level considered safe for a worker, 8 hours a day, five days a week for many years. Conversely, an Exposure Level I (and possibly an Exposure Level II) probably should not exceed short-term exposure limits (STELs) that are set to protect workers from acute effects.

Response: OEHHA agrees that comparing RELs to other published values has some value. However, it is only useful if the reasons for the derivations of the values and the margins of safety are similar in intent and the databases used are the same. The occupational standards developed by the ACGIH are clearly intended for purposes other than community health-based values. Although a description of exposure conditions may be provided, it is often unclear in the ACGIH documentation if workers or others have been exposed at concentrations equivalent to the workplace standard or to levels near the standard. Even the ACGIH acknowledges the limitation of a TLV's utility in the second paragraph of the Introduction section of the TLV document: *"These values are intended for use in the practice of industrial hygiene as guidelines or recommendations in the control of potential health hazards and for no other use, e.g., in the evaluation or control of community air pollution or physical agent nuisances...These values are not intended as fine lines between safe and dangerous exposure concentrations...."*. There is general agreement that using workplace standards as acceptable community standards is inappropriate. Moreover, the TLVs have not undergone peer review, and there is question in some cases about their ability to protect even workers from adverse health effects.

Comment: OEHHA has not used the best method available for deriving acute exposure levels for individual chemicals. Four methods are presented by OEHHA for determining acute toxicity exposure levels: 1) existing exposure guidelines to develop screening "usable" values, 2) a NOAEL approach, 3) a benchmark dose approach, and 4) a categorical regression analysis.

The majority of the acute toxicity exposure levels for individual chemicals presented in the document were developed using Method 1, even when acute toxicity exposure levels have been developed using more comprehensive and scientifically rigorous methods. For example, EPA published Health Effects and Dose-Response Assessment for Hydrogen Chloride Following Short-Term Exposure (EPA, 1992) using Method 4. The model used in the EPA hydrogen

chloride analysis is well suited for use in deriving comprehensive acute exposure limits for other chemicals.

Response: Where appropriate existing acute exposure values were found, OEHHA made use of these values and adopted them ("Method 1").

OEHHA is aware of the USEPA report using categorical regression for determining acute exposure levels for hydrogen chloride. The USEPA report illustrates a novel approach that considers all available data and OEHHA supports the continued investigation of this method for future use. Currently there is no way to statistically validate or measure goodness of fit for this model; therefore it lags behind the benchmark dose as a tested methodology. Furthermore, the USEPA model was constructed before the data on human asthmatic subjects were collected (Stevens *et al*., 1992).

OEHHA has set precedent with proposed benchmark dose derivations by using dose-response data for 13 exposure levels in the technical support document. OEHHA has striven to obtain, review, and use the original published data from available studies.

Comment: No method is proposed for managing completion/revision of RELs or allowance for submission of revised or alternate RELs. In Figure 1 of the draft document, OEHHA outlines the public and peer review process for finalizing the draft document. However, no mechanism is proposed to: 1) finalize or refine the individual RELs that have been submitted in the draft document, 2) set a schedule to internally review and revise RELs as new data become available, and 3) provide a procedure allowing review or submittal of alternative exposure levels derived by external groups.

Response: The RELs have been revised based upon public comments received and new data reviewed. The guidelines will be finalized after approval by the scientific review panel. As is customary for other guideline levels, these guidelines will be updated periodically and improvements in the area of toxicology and risk assessment will be incorporated into the technical support document. OEHHA welcomes the submission of new data or analyses that contribute to greater accuracy in risk assessment at any time. Our intent is to have the acute RELs reflect the best available scientific data.

Comment: OEHHA acknowledges that many of the acute exposure levels are derived from either a preliminary screening of the literature or from existing exposure guidelines that may be outdated or inadequate. In Appendix E of the draft document, OEHHA indicates that literature searches have been completed for less than one-half of the chemicals for which acute exposure limits have been derived; that is, for the majority of the chemicals for which a REL is being released, the first step of reviewing the full extent of the relevant literature has not even begun. OEHHA should devise a method to clearly distinguish to the regulated community the "preliminary" or "interim" RELs from those developed based on comprehensive data review and an integrated analysis.

OEHHA acknowledges that the basis for using a screening approach in deriving acute exposure limits is to save time and money for the agency. To address extensive uncertainties in a screening approach, large margins of safety must be applied, thus unduly lowering the derived exposure limit. However, it will be neither quick nor inexpensive for regulated industries to address the ramifications of meeting OEHHA's "screening" exposure levels. Many industries have already invested much time and money in assessing the potential human health risks associated with routine or accidental emissions. At the least, OEHHA should allow some mechanism for outside experts/scientists to submit exposure limits derived using a comprehensive method for review and consideration as alternative or revised RELs.

Response: OEHHA welcomes the submission of any pertinent data by outside researchers. Each and every chemical in the technical support document underwent a thorough literature search. The RELs are not hastily constructed "screening values". The contracted literature searches (Appendix E) actually served to supplement and enhance in-house literature searches, and are for uses beyond the development of acute RELs. For example, the contracted literature searches for each chemical do not focus merely on acute health effects, but also on chronic, long-term health effects, which comprise a considerably larger database.

Rather than saving "time and money for the agency", the initial adoption of screening values serves to place an accepted guidance level for public consideration while a more detailed and time-consuming analysis of its validity is carried out. Screening values are not proposed in the revised document. The use of appropriate uncertainty factors for such areas as individual variability and interspecies variation should be separated from uncertainty in the quality or completeness of the data upon which these values are based. OEHHA does not apply additional uncertainty factors to account for poor data quality in the document.

Comment: There is a lack of precise definitions for toxicological endpoints for deriving hydrogen fluoride acute exposure levels I and II.

Acute Toxicity Exposure Level I (REL for hydrogen fluoride): OEHHA did not apply the toxicological criteria for Exposure Level I (as outlined in the discussion in the draft document) when deriving an REL for hydrogen fluoride. There are several possible causes for this occurrence, which range from lack of clarity in the exposure level definitions (see general comments) to incorrectly reporting study results. Several of these points are discussed below.

Is the hydrogen fluoride Exposure Level I REL derived as a concentration at which there may be a perception of mild irritation of the eyes, nose or throat, unpleasant odors, tastes or sight, or changes of uncertain physiological significance, but where no minor adverse health effects are observed? This is the definition given in the draft document, page 11. In contrast, the derived REL for HF appears to be based on an uncertainty factor applied to the NOEL for a "discomfort or mild effect level" that is, in itself, not considered an adverse health effect by the REL definition. Is the REL the mild effect level or the NOEL (not NOAEL, as this effect is not considered an

adverse health effect by definition)? Is the 10-fold uncertainty factor for sensitive subpopulations to be applied to the effect level or the NOEL?

Response: As stated in the response to the comment's general remarks, the quote from the technical support document is an error in the document and has been corrected. The REL for HF is based on a NOAEL for upper respiratory and eye irritation. These effects are considered adverse.

Comment: In the published study serving as the basis for the OEHHA REL for hydrogen fluoride (Largent, 1961) it was noted that irritation was "slight" to "very slight" following exposure for 6 hours per day up to 50 days. One of the five subjects did experience discomfort, described as a burning sensation in the nose, while suffering from a head cold during the exposure period. This same subject experienced skin irritation at 3.39 ppm, but not 1.42 ppm. Of the other four it was reported that "Very slight irritation of the eyes and nose, and slight cutaneous irritation were experienced by the other four subjects during the course of their exposures to HF. None of these subjects offered any complaints, and they did not suffer any apparent discomfort even though cutaneous erythema developed frequently." It was concluded that "although signs and symptoms related to the effects of the skin developed during periods of exposures, no systemic effects of a clinical nature could be detected," and "For the relatively brief periods of inhalation and the levels of exposure to HF described here in connection with a total of five human experimental subjects, no adverse effects of any kind were detected." This conclusion was reiterated in a personal communication with Largent (May, 1995). In contrast, OEHHA summarized this study with "Complaints of eye and upper respiratory tract mucous membrane irritation were reported in five individuals exposed to daily 6-hour concentrations of HF." It is suggested that OEHHA provide a summary of a study that is more consistent with the original results. In this case, it is apparent that the effects noted were slight, and that dermal effects predominated over eye and mucous membrane irritation.

Response: The key reference used for the HF REL is now Lund *et al*. (1997); the results from this study are consistent with OEHHA's interpretation of the Largent (1961) study. All of the individuals tested in the Largent (1961) study complained of mucous membrane or dermal irritation. Irritation of the eyes, throat, and skin are considered by OEHHA to be adverse health effects. In absence of published errata, the data presented in this study offer clear evidence of critical endpoints to be used in REL development. The REL changed from 140 to 240 $\mu g/m^3$.

Comment: Based on OEHHA's definition of an acute Exposure Level I, all of the exposure concentrations assessed in the Largent (1961) study are at or below the "discomfort and mild effect level" that will cause no adverse health effects, even when the 6 hours per day exposure periods were repeated for up to 50 days. OEHHA assumed that the onset of irritation occurred during the first hour of the experiment. However, Largent reported in a personal communication (May, 1995) that the "trivial" irritation occurred well after the study was in progress (not within the first hour). Although (and acknowledged by OEHHA) the 1961 study did not state the time elapsed before any effects were noted, some weight should be given to both the length of time the

subjects were exposed (6 hours/day, up to 50 days), and the nature and degree of effects observed. (We will attempt to gain more explicit information from Dr. Largent regarding elapsed time before effects were observed).

Response: The time of onset of symptoms in the Largent (1961) study was poorly reported. Clearly, irritation effects were occurring on the first day since the subjects had to apply protective cream to their skin. Therefore, logical health-protective assumptions were made regarding the onset of symptoms. Although information provided by Dr. Largent would be helpful, OEHHA strives to utilize published, peer-reviewed data in the development of RELs. Although the Largent study was poorly reported, it was considered the best available study for REL development because it used human data. A recent study with improved reporting is now used as the basis for the REL (Lund *et al*., 1997).

Comment: A NOAEL is not the lowest level at which adverse effects are not observed for a given exposure duration. Rather, it is the highest level at which adverse health effects are not observed. Using this methodology, OEHHA should have selected the highest daily exposure concentration from the Largent study as a Level I, not the lowest, especially if an uncertainty factor of 10 is applied to derive an REL that provides additional protection for sensitive populations.

Response: Contrary to the comment, the 1.42 ppm value is the highest NOAEL reported in the Largent study (the concentration at which no health complaints were reported). The lowest LOAEL was 2.59 ppm (health complaints were reported at this concentration). It is not appropriate to select a NOAEL that is higher than a reported LOAEL; therefore the NOAEL of 1.42 ppm was used as the basis for the previous REL. As stated, the key reference for the acute REL is no longer the Largent study.

Comment: OEHHA has proposed a Level II acute exposure level of 1 ppm, based on an animal inhalation exposure study by Rosenholtz *et al*. (1963). Based on reported observations of rats immediately following exposure, "occasional pawing at the nose and blinking of the eyes occurred, but no other signs of toxicity were noted" at 103 ppm for 1 hour (6 percent of the LC50). "Most of these signs were mild and disappeared within a few hours after exposure." At 126 ppm (12.5 percent of the LC50), general discomfort, pawing at the nose, and tearing from the eyes were reported in rats. Dogs exhibited mild ocular irritation, evidence of dermal irritation (e.g., rolling on grass), sneezing, and developed a dry nonproductive cough which lasted two days. Alexeeff *et al*. (1993) identified 126 ppm as a "mild irritation" level. However, OEHHA identified 103 ppm as a NOAEL for severe effects, and then applied an uncertainty factor of 100 to account for interspecies and individual variation, to arrive at an Exposure Level II of 1 ppm.

If Exposure Level II for hydrogen fluoride is an exposure above "which severe irritation to the eyes, nose, and throat would occur", should not the value be derived from a concentration that has actually caused this effect in humans or animals, rather than the NOAEL? Neither 6 percent nor 12 percent of the LC50 for one hour of exposure produced "severe" effects in the Rosenholtz

study. The authors noted that concentrations from "about 7 to 12 percent of the LC50 value were noted to produce minimal clinical signs of toxicity in experimental animals. Furthermore, in our study, no morphologic evidence of tissue damage was seen even at considerably higher concentrations." Only at 25 percent of the LC50, and certainly 50 percent of the LC50, could the observed effects be determined "severe" according to OEHHA definitions. Additionally, use of an animal study to derive a Exposure Level II has resulted in a value (1 ppm) that is lower than the OSHA PEL and NIOSH REL of 3 ppm, and an OSHA STEL and NIOSH ceiling of 6 ppm. These occupational exposure limits were set to protect chronically exposed workers from both respiratory irritation and fluorosis. It is not plausible that a level to which a worker may be exposed day after day could cause a serious disability or injury in a member of the general public after just one hour of exposure.

Response: OEHHA uses human data, if available, for REL development. However, in its absence, animal data are used with appropriate uncertainty factors, as in the case of the severe adverse effect level for HF. The Rosenholtz *et al*. (1963) study showed that a 1-hour exposure to 126 ppm HF in rats resulted in *"general discomfort, pawing at the nose, and tearing from the eyes.... Dogs showed a mild ocular irritation and sneezing on withdrawal and developed a dry nonproductive cough lasting about two days. They also rubbed their noses and bodies on the grass, probably as a result of skin irritation, but no gross lesions were noted."* The animals in this study exhibited signs of moderate irritation to the eyes, nose and skin, lasting several days after exposure. OEHHA considers this effect to be a severe effect level. Therefore, the next highest concentration, 103 ppm, was selected as the NOAEL for moderate irritation. Since humans have complained of irritation at concentrations far below those reported in animals from Rosenholtz *et al*. (Largent, 1961; Machle *et al*., 1934), addition of an interspecies uncertainty factor is justified.

The derivation of the severe adverse effect level value is consistent with OEHHA's statement in the technical support document that REL development will proceed from the highest NOAEL reported.

The ACGIH-TLV of 3 ppm is equivalent to the LOAEL for irritation reported in the Largent study. The TLV is therefore set at a concentration demonstrated to cause adverse effects in humans. The TLV document states that the purpose of the TLV for HF is to "minimize" irritation and fluorosis in occupational settings. On the other hand, the purpose of the REL for HF is to prevent irritation in the general population.

Similarly, considering that the ACGIH-STEL for HF of 6 ppm is a 15-minute value which is not to be exceeded at any time during the 8-hour workday, it seems reasonable that the 1-hour severe adverse effect level for HF, which is intended to protect sensitive individuals, be lower. As stated above, the use of occupational standards for the general public is not appropriate.

Comment: Attachment A provides a list of published human and animal exposure studies that are relevant for deriving an acute, inhalation exposure level for hydrogen fluoride. Several of these studies were not included in the references OEHHA cited, underscoring the necessity of

conducting a complete literature review. It is acknowledged that no individual study (human or animal) is adequate for deriving a one-hour acute toxicity exposure level. However, we believe the collective human and animal data are sufficient to derive an acute exposure level using a categorical regression analysis (OEHHA risk assessment method 4).

Response: OEHHA did not include every available reference on hydrogen fluoride in the summary document, only those that were critical to understanding the toxicity of HF or those references critical for the derivation of the REL. We appreciate the contribution to the very marginal literature for HF toxicity. However, two of the references cited are based on the same data (e.g., Wing *et al*., 1991; and Ibert, 1987). In these cases, the peer-reviewed published work (Wing *et al*., 1991) has already been cited in the technical support document in lieu of the other report. Other references (e.g., NIOSH, 1976; U.S.EPA, 1988; ACGIH, 1986) were secondary references that we reviewed but did not incorporate into the summary as they contained no new information. Six of the references in the comment's suggested bibliography (AIHA, 1988; Higgins *et al*., 1972; Largent, 1961; Rosenholtz *et al*., 1963; Wing *et al*., 1991; and Wohlslagel *et al*., 1976) are already described in the OEHHA document. The preliminary unpublished data by Haskell Laboratory (1988) was not summarized since several published rodent lethality studies existed and were reported in the summary. Finally, many of the other references do not address the acute toxicity of HF, but instead examine the effects of fluorine or a mixture of breakdown products from uranium hexafluoride degradation. These references, although somewhat related, were not pertinent to the toxicity summary for HF. Such data would therefore be inappropriate for REL development.

OEHHA has previously reviewed the categorical regression method of data analysis, and the technical support document mentions this as an option to be considered in the future.

Comment: The lowest average exposure concentration in the Largent study was 1.42 ppm rather than 1.42 mg/m^3. The REL derived by OEHHA's methodology should therefore be 0.142 ppm (0.118 mg/m^3). We suggest OEHHA confirm all air concentration units and calculations in Appendix C against the supporting literature prior to finalizing the Technical Support Document.

Response: The units for this calculation were reversed as stated in the comment and have been corrected. OEHHA appreciates the thorough review of the summary for HF.

Comment: Based on our critique, we conclude that the draft document is: 1) preliminary, 2) lacks a clear description of toxicological endpoints, 3) lacks sufficient detail regarding [how] toxic endpoints are applied in the derivation of levels, and 4)contains too many fundamental inconsistencies to be released as a final guidance at this time. Specifically, we request the following be provided in the final guidance:

Precise definitions of "adverse health effect", "adverse effect", and "mild effect"

Response: The inconsistency in the definition of mild (Level I) effect has been corrected in the technical support document as explained in response to comment by Harding-Lawson. The precise definitions of adverse health effects considered for the different levels is provided in Table I of the technical support document. "Effect" is considered synonymous with "health effect".

Comment: We request a precise description of whether the NOEL, NOAEL, LOEL, or LOAEL will be used as the basis of deriving an acute exposure limit, and what the potential implications will be in terms of margins of safety and uncertainty

Response: As stated in the Technical Support Document in the section titled "Risk Assessment Methods - No Observed Adverse Effect Level Approach", the highest NOAEL is the intended starting point of the REL in cases where benchmark dose calculations are not possible. If a study contains only a LOAEL, the lowest LOAEL is used. There is no practical distinction between NOAEL and LOEL in this case, as stated in the technical support document under the Risk Assessment Methods section: *"The concentration which produces biologic effects that are not considered adverse may be termed the lowest effect level (LOEL); this is identical to the NOAEL (USEPA, 1990)."* The NOEL does not relate to adverse effects and therefore is not used in the determination of RELs.

Comment: We request a more detailed description of the regulatory uses to which these values will be applied.

Response: See the Technical Support Document under "Objective". This language in this section has been revised and now better describes the Air Toxics Hot Spots statute and the requirement of OEHHA to produce risk assessment guidelines, including those for acute non-cancer effects.

Comment: We request a method for distinguishing interim "screening" values from final values derived through consideration of the literature and a more comprehensive methodology.

Response: All of the values in the document are draft final values in this iteration of the Document, the Draft for Public Comment. There are no "screening" values in this document. As previously discussed, in response to a previous comment in this set of comments, new data have been considered and revisions made to RELs based on public comments received. The revised document will be distributed for public comment and to the SRP. Revisions will be made following receipt of comments from the SRP. A "final" document will then be released for use as described in the technical support document.

Comment: We request a plan and schedule for prioritizing the finalization of the interim values.

Response: As stated above, there are no "interim" values. The schedule has been described above.

Comment: We request a schedule for reviewing new, relevant, published data as it becomes available and possibly updating and revising existing values

Response: OEHHA accepts the submission of new toxicity or epidemiology data pertaining to REL development on an ongoing basis. OEHHA does not currently have a projected time for the next update of this document. We anticipate annual updates after our risk assessment documents have been finalized.

Comment: Finally, we request that OEHHA provide a mechanism for external experts to submit revised or alternative RELs for review, consideration, and possible incorporation into the guidance.

Response: As stated above, we welcome submission of new data or analyses of data that may better our understanding of the toxicity of specific chemicals. If, after review, the data suggest that certain RELs be changed, then the changes will occur in the next update of the Technical Support Document.

Metal Finishing Association of Southern California

Introduction

Comment: When quantitative risk assessment is done, methods other than the outmoded, unmodified default uncertainty factors should be used; there is a very large literature available that recommends methods that make use of toxicologic information for the extrapolation of risk to humans. California, a leader in so many things, should not use obsolete methods for estimating risk. Furthermore the "level" (I or II) should be taken into consideration when "Hazard Quotient or Hazard Index" is calculated so that regulatory agencies will distinguish between "discomfort or mild effect" and "disability or serious effect". This document is intended to help provide a scientific basis for recommending exposure levels that will be protective for 1-hour acute, inhalation exposure to $NiSO_4$. It addresses the points summarized above.

Response: OEHHA's methodology is a synthesis of currently accepted practices (uncertainty factor approach) that have been used successfully for decades by a host of federal and state agencies, together with the newer benchmark dose methodology which attempts to reduce uncertainty through consideration of dose-response information. It is accepted that the uncertainty factor methodology is an imperfect approach. However, the data requirements for benchmark dose are substantially greater than that for the uncertainty factor method. It is therefore only useable with a subset of chemicals, not with all chemicals that OEHHA must address. As benchmark dose methodology improves (e.g., methods for considering continuous data are developed), OEHHA documents will evolve correspondingly.

The relative severity of the Level I vs. Level II effects is clearly indicated in the Technical Support Document and in the Guidelines. This information is available for risk managers to take into account and OEHHA staff are available for consultation when making such complicated decisions.

Comment: RELs For Different Nickel Compounds

Different inorganic nickel compounds have differing toxicities. Since toxic effect is a function of concentration at the biologic target site and since absorption and distribution in the organism are determined by the chemical and physical characteristics of each chemical species, the recommendation of exposure controls based solely on nickel content is inappropriate. Benson *et al*. (1987 and 1988) make the point that pulmonary retention is a function of solubility. In their work they reported that during exposure to nickel subsulfide concentrations equivalent to 7 mg Ni/m^3, lung accumulation was 7 times greater than during exposure to the nickel-equivalent amount of nickel sulfate. Furthermore, in their study nickel sulfate lung burdens did not increase with duration of exposure as did nickel subsulfide. The authors attribute these findings to the difference in solubility of these two chemical species. English *et al*.(1981) found that after intratracheal injection, nickel chloride was excreted primarily in the urine while nickel oxide was equally excreted in the feces and urine. The oxide persisted in the lung for more than 90 days while the chloride was rapidly excreted from the lung, with greater than 50% of the nickel cleared

within 3 days. NTP (1994) p 21, summarizes the absorption and distribution of nickel: "in absorption and distribution studies for nickel administered intratracheally or by inhalation exposure, the lung half-life was 1 to 3 days for nickel sulfate, 5 days for nickel subsulfide, and greater than 100 days for nickel oxide. Nickel was detected in extra-respiratory tract tissue after exposure to nickel sulfate or nickel subsulfide, but not after exposure to nickel oxide." The short biological half-life of the soluble nickel compounds although not so important for short irritant exposures, does allow the conclusion that intermittent, acute exposures are unlikely to lead to cumulative effects. We conclude from the above that it is entirely scientifically justifiable to request that different RELs be developed for different nickel compounds and that is appropriate for us to focus our attention upon the specific characteristics of nickel sulfate.

Response: Soluble and insoluble nickel compounds have very different toxicodynamics. This point is recognized and discussed briefly in the Technical Support Document on Nickel, page 2. The rapid elimination half-life of soluble nickel (several days) is an important consideration for cumulative or long-term effects. However, it bears little significance when considering short-term, mild reversible effects. There is therefore no justification for discounting soluble nickel acute toxicity based on elimination half-life. Finally, although OEHHA agrees that there is scientific justification for considering soluble and insoluble nickel separately for the purposes of non-cancer health effects, there is no hypothesis nor scientific justification for considering nickel sulfate differently from other soluble nickel compounds. Furthermore, although there is justification for speciation based on toxicodynamics, there are insufficient inhalation studies on insoluble nickel compounds for the relevant endpoint (respiratory irritation or immunotoxicity) to allow for development of separate acute RELs for different nickel compounds.

Comment: Immune System Effects to Measure Inhalation Health Effects for Nickel sulfate

The immune system effects as reported by Graham *et al*.(1978) should not be used for the risk assessment of nickel sulfate. In their study they reported that inhalation exposures to $NiCl_2$ at the 250 μg Ni/m^3 and higher concentrations caused immunosuppression of spleen antibody forming cells as measured by a hemolytic-plaque technique. A linear dose response relationship was seen. However nickel sulfate was not used in the inhalation part of this study but was given intramuscularly as were $NiCl_2$ and NiO. $NiS0_4$-$6H_20$ at 3.09 μg Ni/g showed immunosuppression while $NiCl_2$ only showed immunosuppression at 9.25 μg Ni/g and above. But neither $NiSO_4$ or NiO showed a dose response relationship for splenic immunosuppression; only $NiCl_2$ did.

Response: While it is true that nickel oxide produced no immunosuppression by injection and also was not tested by inhalation, the same can not be said for nickel sulfate. All doses of nickel sulfate tested by intramuscular injection in Graham *et al*. (1978) significantly suppressed the antibody response, with maximum suppression of up to 55%. The authors suggest that nickel sulfate is 3 times more immunotoxic than nickel chloride when compared on the basis of nickel content, possibly due to toxicity of excess systemic sulfate anion.

Comment: The Graham *et al*. (1978) study was a follow-up of a study by the same group published in 1975 (Graham *et al*., 1975) in which mice were injected intra-muscularly (IM) with suspensions of nickel chloride in the amounts of 3.09, 6.17, 9.26 and 12.24 μg Ni/gram of body weight. The hemolytic plaque technique which they used for measuring systemic immunosuppression was positive for $NiCl_2$ at doses of 6.17 and above in this study but in the later (1978) study 9.25 μg/g was required for immunosuppression. The discrepancy in effective dose for $NiCl_2$ between the two studies was not addressed by the authors but probably is attributable to the inherent susceptibility of this test to small changes in the handling of the animals. Differences in dose requirements for systemic immunosuppression as measured by Ni content between $NiCl_2$ at 9.25 μg Ni/g and $NiSO_4$-$6H_2O$ at 3.09 μg Ni/g reported by Graham *et al*. (1978) may also represent difficulties with the test or could possibly reflect differences between these two soluble chemical species of nickel.

Response: The comment raises concerns about the repeatability of the immunosuppression results for nickel chloride between the Graham *et al*. (1975) and Graham *et al*. (1978) studies. Specifically, a discrepancy between a statistically positive result at 6.17 vs. 9.25 μg/g is described in the comment as a sign of the inconsistency of the endpoint. However, a closer examination of the data reveals that the results of the two studies are actually remarkably similar. The mean number of plaques/10^6 spleen cells is nearly identical between both studies at all doses when comparing the effects of injected nickel chloride. The two studies were conducted several years apart, and used different statistical methods to separate means in the analysis of variance (Williams test vs. Duncan's multiple range). Both the authors of the paper and OEHHA staff conclude that the results of the second study are supported by the similar findings in the first study.

Comment: In a further effort to understand the effect of Ni on immunosuppression, NTP supported a 12-day inhalation study which exposed rats and mice to $NiSO_4$ $6H_2O$ at concentrations, measured as Ni, of 780, 1,560, 3,350, 6,700 and 13,400 μg/m^3 (Benson *et al*., 1988). In mice the only level tested that did not kill all of the test animals was the lowest dose, 780 μg/m^3. This dose failed to cause changes in systemic immunity as measured by spleen natural killer cell activity or spleen atrophy. An additional NTP-supported inhalation study in mice exposed to $NiS0_4$ $6H_20$ as well as two other inorganic nickel compounds, nickel oxide and nickel subsulfide, was conducted by Haley *et al*. (1990). In this study exposures were for 13 weeks at exposure levels, measured as Ni, of 27, 110, and 450 μg/m^3. At none of the $NiSO_4$ $6H_2O$ dose levels was there a significant change in systemic immune function, as measured by changes in spleen antibody-forming cells, changes in spleen natural killer cell activity, or change in mixed lymphocyte response. A non-significant trend in spleen antibody-forming cells was seen at the 450 μg/m^3 level.

Response: The Benson *et al*. (1988) study, which established a 12-day NOAEL for lethality of 780 μg/m^3, used a small sample group size (4-5/group) and did not measure the antibody response, but only natural killer cell activity. Natural killer cell activity involves cellular and physiological mechanisms different from an antibody response, therefore a direct comparison of the two endpoints is invalid. Furthermore, the antibody response is a much more sensitive and

representative indicator of overall immune dysfunction than natural killer cell activity (Luster *et al*., 1992).

The Haley *et al*. (1990) study examined the effects of nickel oxide, nickel subsulfide, and nickel sulfate on several immunological tests. This study showed a non-statistical trend for decreased splenic antibody response in mice exposed for 90 days to nickel sulfate. Statistically significant decreases in the antibody response and other immune functions were seen following inhalation of either of the insoluble forms of nickel. However, nickel sulfate was tested at lower Ni^{2+} concentrations than either nickel oxide or nickel subsulfide. Additionally, unlike the short-term nickel studies by Graham *et al*. (1975, 1978) and Adkins *et al*. (1979), 3 days elapsed after termination of exposure and before the antigenic challenge. Mice were then necropsied 1 week after nickel exposure and numbered 7-10 per group. As stated above, it is not appropriate to compare natural killer cell activity to antibody response data. The same can be said for the mixed lymphocyte response, which only measures T-lymphocyte proliferation in the presence of foreign histocompatability markers. Significantly increased cellularity was present in the lymph nodes and lavage fluid of mice exposed to any of the 3 nickel compounds. The authors of the Haley *et al*. (1990) study conclude from their study: *"We conclude that the inhalation of nickel compounds at occupationally relevant concentrations can result in significant alterations of pulmonary and systemic defenses."*

In summary, neither of the above studies refute the findings of immunotoxicity of nickel compounds. Although these studies have weaknesses (study design, excessive mortality and endpoints measured), the findings lend support for the consideration of nickel as an immunotoxicant.

Comment: Thus, in the two nickel sulfate hexahydrate inhalation studies in mice conducted subsequent to those of Graham *et al*.(1978) efforts to reproduce systemic immunotoxicity following inhalation exposure have been unsuccessful. NTP (1994) reviewed the work of Haley *et al*.(1990) and concluded that systemic immunity was not altered by exposure to nickel sulfate hexahydrate.

Response: There is insufficient evidence to categorize nickel sulfate separately from nickel chloride or other soluble nickel compounds. Nickel sulfate showed distinct suppression of the antibody response at all levels tested when animals were exposed to nickel intramuscularly (Graham *et al*., 1978). In addition, mice exposed to nickel chloride or nickel sulfate by inhalation were significantly more susceptible to streptococcal infection than controls (Adkins *et al*., 1979). The decreased host-resistance in Adkins *et al*. (1979) is significant since exposure to soluble nickel compounds was only for 2 hours, and since the outcome is consistent with the immunotoxicity findings of Graham *et al*. (1978).

Comment: The mouse is a good model for the study of systemic immune effects. However, efforts to correlate findings in this model with clinically significant changes in the human have not been rewarding. On both grounds, the inability to substantiate the Graham *et al*. (1978) findings,

and the absence of good clinical correlation, risk assessment based on mouse systemic immunosuppression is inappropriate.

Response: There have been few attempts to correlate immunotoxicity results in the murine model to human clinical effects and epidemiological data do not exist at all. There are several reasons for this data gap. First, it is not a trivial matter to measure an antibody response, or any other aspect of immune system function of humans following exposure to an immunotoxicant. Many of the assays performed in laboratory animals are invasive and are often even lethal. Epidemiological research on occupational or population-wide immunological functions in response to chemical exposure has not been done, although USEPA and NIOSH are currently conducting pilot studies which aim to fill this gap (Dr. M. Selgrade, USEPA, personal communication, February 1995). Since the immune system is affected by many environmental factors, epidemiological studies of specific immunological effects of environmental chemicals are extremely difficult. Furthermore, a paper by Selgrade *et al*. (1995) documents several cases in which animal immunotoxicity data is predictive of similar effects in humans following exposure to well-known immunotoxicants (UVB radiation and ozone).

Comment: The Target Organ for Measuring Risk

We wish to call attention to the lung and respiratory tree as the appropriate target for risk assessment. There is one very important human study that may serve as a basis for risk assessment. Cirla *et al*. (1985) report a study of 12 metal plating workers admitted to an occupational health clinic for complaints of respiratory distress. Of these, 7 were diagnosed as having occupational asthma induced by exposure to nickel. Challenge testing with a 0.3 mg/m^3 nickel sulfate aerosol resulted in significant lowering in FEV_1 for 6 of the 7 subjects. Challenge testing was not done at lower doses. Asthmatic subjects without history of nickel exposure did not respond to the challenge test. The 0.3 mg nickel sulfate (67 $\mu g\ Ni/m^3$) represents the lowest acute human exposure for which a response has been documented in sensitized individuals. The value of this study to the issue of attempting to estimate a 1-hour acute, non-carcinogenic REL is that it provides information from a well measured exposure dose delivered over a short time period to the most sensitive members of the human population. Extrapolation from a low observed adverse exposure level for a transient effect would be the only step needed to give a meaningful acute, non-cancer REL.

Response: The study by Cirla *et al*. (1985) is a useful study in identifying pulmonary reactions in sensitive asthmatic nickel-sensitized subjects exposed to soluble nickel. The study is mentioned in the Technical Support Document. The data from Cirla *et al*. (1985) are weakened by the absence of a NOAEL in these subjects, and by the small group size of 7 subjects. However, since these are the best available data in sensitive human subjects, and since a large degree of uncertainty exists in estimating the immunotoxic effects of nickel in humans, OEHHA agrees with the comment that this study should replace the Graham *et al*. (1978) study as the basis for the REL for nickel. The 1-hour REL has been recalculated on the basis of the Cirla *et al*. (1985) data, incorporating an uncertainty factor of 10 for the lack of an experimental NOAEL, and the REL thus changes from 1.6 to 3.3 $\mu g/m^3$. This will be added to the Technical Support Document.

Comment: In addition to human studies, there are a large number of well conducted animal inhalation studies in which the effects of nickel sulfate exposures on the respiratory system were analyzed.

Response: OEHHA agrees that the lung is a primary target organ for the toxicity of nickel compounds, particularly with longer term exposures.

Comment: The confirmation that pulmonary damage seen at the 0.5 mg/m^3 level in rats has a significant functional effect on an animal's ability to defend itself from external threats is provided by the study of Adkins *et al*.(1979) in which a 2-hour exposure to nickel chloride at a Ni-equivalent dose of 0.499 mg/m^3 caused mice to be susceptible to streptococcal infections with increased mortality.

Response: The results of the Adkins *et al*. (1979) study, which show a clear dose-dependent influence of soluble nickel compounds on resistance of mice to mortality from streptococcal infection, are consistent with compromised systemic immunity in addition to non-specific damage to lung tissue. Pulmonary damage was not observed in the Adkins *et al*. study following the brief 2-hour exposure. It therefore seems unlikely that pulmonary damage accounted for the increased mortality effect. Lavage fluid cell analyses from these mice similarly showed no effect from nickel exposure, which emphasizes that lung inflammatory changes were not responsible for the increased bacterial susceptibility in the Adkins *et al*. study. The authors of the Adkins *et al*. study recognized that systemically compromised immunity, as observed in the Graham *et al*. (1975, 1978) and other studies, most likely contributed to the decreased host-resistance and consequent mortality.

Comment: Concern for Risk Assessment based on Systemic Absorption

If the decision is made to base risk assessment for acute Ni exposures on systemic effects, consideration should be given to the contribution of diet to daily Ni intake and its relationship to any proposed REL. Dietary amounts have been variously estimated to be in the range of 150 μg/day by Flyvholm (1984) or 288-696 μg/day by Murthy (1973). With an absorption rate from the GI tract of between 3% and 10% this still represents a significant uptake. At higher dietary levels, above 200 ppm, toxicity to the mechanism that controls GI absorption occurs.

Response: Because the systemic toxicity of nickel varied by route of exposure in the Graham *et al*. (1978) study, it is probably not appropriate to compare results across routes of exposure. The REL presented in the Technical Support Document is for the inhalation route of exposure only.

Comment: A further complication to setting a REL based on systemic absorption is the fact that Ni has been shown to be an essential micronutrient for a number of mammalian species and may

be essential in humans, although this is difficult to show since Ni's widespread presence in foods, makes it difficult to produce a deficiency state under study conditions.

Response: As the comment indicates, the human requirement for nickel cannot be definitively proven with current scientific knowledge. However, regardless of the significance of nickel in the diet, inhalation of nickel has a variety of adverse local and systemic effects. These effects should not be ignored unless it can be shown that the effects are spurious results or that they are not pertinent to human health.

Conclusion

Comment: We believe that the Agency's non-carcinogenic REL of 1.6 μg Ni/m^3 for only a one hour exposure for all inorganic nickel compounds is not scientifically responsible. Risk assessment and REL should be based on effects of nickel sulfate to the lung and data from the study of sensitized humans is probably the best basis for a nickel sulfate REL.

Response: OEHHA has responsibility to account for and consider all valid toxicological and medical data in generating RELs for airborne toxicants. However, there is inadequate evidence for disregarding the immunotoxic effects of nickel compounds in several studies and several species.

The use of the pulmonary reactivity in asthmatic nickel workers is a constructive suggestion and OEHHA appreciates the contribution to the acute REL development process. Since only soluble nickel was tested in this study, the REL will remain applicable for all nickel compounds. There is no scientific justification and there are inadequate data to allow nickel sulfate to be considered toxicologically different from nickel chloride or other soluble divalent nickel compounds.

Reference:

Selgrade MK, Cooper KD, Devlin RB, Loveren H, Biagini RE, Luster MI. Symposium overview: Immunotoxicity - Bridging the gap between animal research and human health effects. Fundam Appl Toxicol 1995;24:13-21.

Monsanto Company

TECHNICAL COMMENTS ON CALIFORNIA DRAFT RISK ASSESSMENT GUIDELINES FOR ACUTE NON-CANCER HEALTH EFFECTS

Comment: Overall, the 1-hour RELs that have been developed by OEHHA are extremely low and are in some cases below chronic limits established by other governmental organizations, i.e., ACGIH Threshold Limit Values (ACGIH, 1995) and the U.S. EPA Reference Concentrations (IRIS database, 1995). In Document II, OEHHA claims to have followed the recommendations in the NAS report, Science and Judgment in Risk Assessment, "by establishing uniform, science based guidelines to be used in the derivation of acute toxicity exposure levels applicable to the general public for hazardous substances released into the environment." However, the values developed misrepresent the science of toxicology because in many instances levels that are considered to be protective of exposures over a life-time are not considered protective of acute 1-hour exposures. For example, we have compared OEHHA RELs to the current TLVs, ERPG-l and ERPG-2s (Emergency Response Planning Guides, American Industrial Health Association) for the first 20 individual compounds from Table 1 in Document I. For 15 of the 19 compounds, OEHHA's RELs are lower than the TLVs and for the remaining 4 compounds the RELs are equal to the TLV. All the RELs are lower than ERPG-1 and ERPG-2 and in many cases lower by more than 2 orders of magnitude.

Response: The comment expresses concern that OEHHA's RELs are not equivalent to other published values from various sources. The comment makes a series of comparisons between OEHHA's RELs and other published values to illustrate the concern that OEHHA uses a methodology that is too conservative. This misrepresents the OEHHA document as explained below.

First, it must be recognized that OEHHA's RELs are based upon the best available dose-response data, and not necessarily on the exposure values published by various organizations. OEHHA has reviewed existing TLVs and ERPGs and has found them to be deficient in certain areas pertaining to adoption of RELs. For example, they often do not consider all available toxicological data and are not applicable to the general population. Furthermore, most other values do not apply consistent methodologies to arrive at health-protective acute exposure values. In these respects, neither the occupational standards, nor many of the ERPG values sufficed for the purposes of establishing RELs for the Air Toxics Hot Spots risk assessment program.

The occupational standards developed by the ACGIH are clearly intended for purposes other than community health-based values. They are sometimes technology-based rather than health-based. Some individuals experience frank, adverse health effects at a TLV, such as the 5 ppm TLV for hydrochloric acid. Even ACGIH acknowledges the limitation of the TLV's utility in the second paragraph of the Introduction section of the TLV document: *"These values are intended for use in the practice of industrial hygiene as guidelines or recommendations in the control of potential health hazards and for no other use, e.g., in the evaluation or control of community air pollution or physical agent nuisances...These values are not intended as fine lines between safe and dangerous exposure concentrations...."*. Most public health scientists agree that using workplace

standards to set acceptable community standards is inappropriate and misguided. The TLVs are designed to protect healthy workers and not the infirm, infants and children, pregnant women, or elderly. Thus, the two sets of values cannot be directly compared.

Although the ERPG values created by the AIHA often use methodology that is difficult to reproduce, they have some potential utility in this process because these are also short-term exposure values. OEHHA has incorporated ERPG values into the technical support document whenever appropriate. A thorough review of all applicable ERPG values prompted OEHHA to send detailed comments concerning several of these values to the ERPG committee. Many of the ERPG documents are incomplete reviews of the literature, contain incorrect citations and have no defined method or rationale for each specific value. Finally, incorporation of any consistent margin of safety, even to the results of animal studies, is a rarity in the ERPG values.

Comment: For 13 of the 54 compounds evaluated by OEHHA, RfCs are also available. As shown in Table 2 (provided by commentator), for 2 of 13 compounds, the REL is either equal to or less than the RfC and for 4 other compounds the REL is within an order of magnitude of the RfC. RfCs are considered to be protective of even the most sensitive individuals for lifetime exposures (24 hours/day for 70 years). In addition for 6 other compounds (nitrogen dioxide, ozone, hydrogen sulfide, carbon monoxide, sulfates and sulfur dioxide) of the 54 chemicals, the 1-hour REL has been set at the California Ambient Air Quality Standard. Again, setting 1-hour exposure limits equal to chronic ambient air quality standards is contrary to established scientific principals.

Response: The acute REL proposed by OEHHA for ethylene glycol monoethyl ether (EGEE) is $\underline{8.8 \times 10^2}$ $\mu g/m^3$, not 2.3×10^1 as shown in the Table 1 of the comments. Furthermore, in the one case that the REL is lower than the RfC (for EGEE), the RfC is based on male reproductive toxicity, as compared to the adverse developmental outcomes described in the acute REL derivation. To scientifically compare the two values, one must consider the endpoints used to derive the numbers. Comparisons of numbers generated by different organizations for various uses has some utility, but can be misleading unless the reviewer closely examines the scientific bases for the values.

Although reproductive toxicity studies use exposure periods for the duration of the critical gestational period, adverse developmental outcomes may occur following a single exposure at a crucial time. Adverse developmental outcome is the critical effect considered in developing the acute REL. On the other hand, the male reproductive endpoints used as the basis for the RfC (decreased testes weight and testicular degeneration) resulted from subchronic exposure (13 weeks). Thus, the values for the acute REL and the RfC cannot be directly compared because the studies and the toxicological endpoint underlying the numbers differ.

The RELs based on California's Ambient Air Quality (CAAQS) values are those values for which a health-based 1-hour CAAQS exists. <u>Annual average CAAQS values were not used in this document</u>. In one case, sulfates, the 24-hour CAAQS was extrapolated to a 1-hour exposure using Haber's relationship.

Comment: OEHHA claims to have followed the recommendations of the NAS Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances (NRC, 1993) for developing acute exposure guidelines; however, one critical aspect of the NAS method appears to have been ignored. As per NAS, the final value should reflect a weight-of-the-evidence review of all available information and a scientific consensus. The numbers developed by OEHHA fail this test in that for many of the chemicals the RELs are not reflective of the scientific consensus regarding the toxicity of the material.

Response: The lack of any specific examples creates difficulty in responding to this comment. In keeping with the NAS Guidelines, the RELs proposed by OEHHA undergo internal review, public review, and review by the California Air Resources Board's Scientific Review Panel before adoption. Specific issues regarding individual chemicals are therefore discussed at many levels prior to adoption.

Comment: The uncertainties associated with estimating acute effects are not as great as those for estimating chronic effects and, therefore, other national and international agencies have appropriately not applied each of these factors when developing acute exposure limits. The National Research Council (NAS, 1993), AIHA and NIOSH have each come to this same conclusion.

Response: OEHHA was not able to find this information in the references cited. The NAS explicitly states in their executive summary (NAS (1993), executive summary, p. 6) that *"It is vital to select uncertainty factors that reflect the quality and relevance of the data, differences between test species and humans, and variation within the human population. Typically, in the past the permissible human exposure has been reduced by a factor of 10 for each additional source of variation or uncertainty."* In cases where specific information existed on sensitive individuals, OEHHA used smaller uncertainty factors. For example, the sulfuric acid REL has a UF of 1, since the study forming the basis of the study was conducted on individuals with asthma, and since a relative wealth of data exist on the acute respiratory effects of sulfuric acid in these individuals.

Comment: Many scientific groups have analyzed each of the uncertainty factors based on existing toxicity studies and suggested that 10 may be an upper bound and 3 is the median value for each of the uncertainty factors. For example, using acute toxicity data, Dourson and Stara (1983) determined that a factor of 3 is sufficient for accounting for intra-species differences.

Response: The Dourson and Stara paper (1983) clearly shows that a 10-fold uncertainty factor is appropriate for intraspecies uncertainty. This point is summarized on page 228 of that paper: *"From this brief presentation of data it seems somewhat reasonable to employ a 10-fold uncertainty factor to account for intraspecies variability in lieu of chemical-specific toxicity data."*

Comment: We have recently evaluated inter-species differences based on results of toxicity studies in multiple species and have shown that the median value for differences between rat, dog and mouse species for chronic and subchronic effects is approximately 3. A copy of our paper which is being submitted to Journal of Human and Ecological Risk Assessment is attached (Attachment I).

Response: OEHHA appreciates the submission of this information and encourages such analyses of areas of uncertainty. Although data on acute exposures is not supplied, from the information presented, it appears that an uncertainty factor of 10 is sufficient in most, but not all cases for estimating interspecies variability and that this would seem to support OEHHA's and NAS's Guideline methodology. OEHHA looks forward to the peer review and publication of these data.

Comment: Furthermore, three different groups of investigators (Weil and McCollister, 1963; Nessel *et al*., 1993; Webb *et al*., 1993) have shown that the average ratio of the LOAEL to NOAEL is approximately 3. It may also not be valid to treat each of the uncertainty factors as independent variables. Indeed, Calabrese and Gilbert (1993) have suggested that the interspecies extrapolation Uncertainty Factor and the intraspecies Uncertainty Factor, UFH, are not totally independent and have recommended modifications in the current U.S. EPA approach based on the concept of interdependence of UFs. This concept is also discussed in Attachment I.

Response: Uncertainty factors, by their very nature, have some degree of conservatism in them. In protecting public health, it is necessary to account for those cases that occur at the tail end of the probabilistic curve as well as the "average" person. This same philosophy governs the use of uncertainty factors. Using the attached information provided by the comment (Nair *et al*., unpublished data, 1989), it is clear that an uncertainty factor of 3 does not provide an adequate margin of safety in many situations. For example, in Figure 2 comparing mice and dogs, an interspecies UF of 3 would only be adequate in 17/30 cases, or 56% of the time. A comparison between rodents and humans would likely show even greater discrepancies due to greater differences in body weight, metabolism, toxicokinetics, excretion and other factors. It is true that uncertainty factors may not be completely independent, even though they are treated as such when multiplying them together. OEHHA encourages efforts such as those referenced and described in the attachment to quantitatively define methodology that more accurately describes the degree of overlap. We have decreased the default UF of 10 to 3 for estimation of a NOAEL from a LOAEL in certain cases. However, at this point, the analyses presented in the comment are insufficient to change our methodology.

Comment: Overall, we believe that acute levels should not be developed using a standard approach of applying a factor or 10 for each of the uncertainties as proposed by OEHHA. We believe if uncertainty factors are used, a range of uncertainty factors should be considered. The magnitude of the individual uncertainty factors should be based on the extent and quality of available data. The selection of the critical study should be done using a consensus approach as is

used for setting other exposure limits like the ACGIH TLVs or the AIHA ERPGs. We also strongly believe that human data should be given preference to data in other species. In addition, once an acute limit is developed, it should be compared to other acute and chronic limits. If l-hour acute limits are equal to or within an order of magnitude of chronic lifetime limits, they should be deemed suspect and undergo further scientific evaluation before being issued as guidance.

Response: OEHHA agrees that only using a factor of 10 is too limiting and may ignore contributions made by chemical-specific data. For this reason, the technical support document uses uncertainty factors in the range from 1-10, depending on available data. For example, in benchmark calculations the interspecies UF for animal studies and the intraspecies UF for human studies has been changed to 3.

OEHHA agrees that human data should be given special consideration and this is also consistent with the NAS Guidelines. For this reason, 33 of 45 (73%) Level I REL values in the technical support document are based solely on human data. Comparing OEHHA's values to other standards may be useful, but should be done with caution since not all values are created for equivalent purposes.

Comment: In some cases, OEHHA has applied a benchmark dose (BMD01) procedure to derive a concentration producing a 1% response and then applied uncertainty factors of 30 to a 100 to obtain an REL. OEHHA selection of BMD01 is well below response levels values that have been recommended in other forums; for example, the International Life Sciences Institute (ILSI)/Risk Science Institute report on the Workshop on Benchmark Dose which was sponsored by U.S. EPA, ILSI and the American Industrial Health Council (AIHC) and included scientists from government, industry and academia, recommended that BMD05 or BMD10 could be used for extrapolating to a reference dose/concentration. A copy of the ILSI report is attached (Attachment II). Thus, we believe if the benchmark dose approach is used, California should use the BMD05 or BMD10 as the starting point for the extrapolation to RELs and then apply a range of uncertainty factors as proposed above.

Response: OEHHA has cited Barnes *et al*. (1995) in the technical support document. The report concludes that the BC_{05} or BC_{10} levels are more appropriate than BC_{01}. The data presented in support of this conclusion appear to focus on the ability of multiple models to predict similar responses in this range, and on the similarity of BC values to NOAELs from developmental toxicity studies only. Since the benchmark analysis is a scientific improvement over the older NOAEL methodology, the scientific rationale in judging benchmark calculations by their ability to approximate NOAELs is questionable. An analysis by Alexeeff *et al*. (1993) using the Probit model showed that the 1% response rate was consistent across multiple models using 4 different chemical data sets. There is no presentation of data set analysis which substantiates the use of BC_{05} over BC_{01} in the ILSI report other than a comparison to developmental NOAELs, and in the OEHHA document, the use of a 1% vs 5% response rate results in a much smaller difference than implied in the ILSI report. In fact, the overall difference between the 95% lower confidence limit on a BC_{01} vs. a BC_{05} in the OEHHA TSD is on average only about 1.3 when using the probit

model. Because of these issues, OEHHA maintains that a BC_{01} may still be an appropriate measure of a practical population threshold for many acute endpoints. A substantial amount of analysis should be done in this area. However, in order to align with the published position of federal EPA and other experts, OEHHA has decided to adopt the BC_{05} as the benchmark. The BC_{01} will also be included for the information of the reader.

Comment: In addition to comparisons to existing standards, we have tried to determine the ability of a small chemical operations to achieve fence-line concentrations at or below those proposed by OEHHA. A small hypothetical plant with 177 sources of fugitive emissions (valves, flanges, pump seals, etc.) was used as the basis for calculating fence-line concentrations that would be expected from routine emissions. Fugitive emission estimates from these source points were estimated using the protocol documented in a technical paper by Schroy, 1986. The resulting downwind concentrations at the fence line (100 feet from source) were estimated using the PHAST v4.2 computer program (DNV Technica, 1993). Eight chemicals were chosen as being representative of those on the California list. The chemicals and the corresponding Reference Exposure Levels (RELs) are presented in Table 3. Many users of chlorine and hydrogen cyanide will find it very difficult to achieve fence-line concentrations below the REL values presented in Table 3. If the fence line were only 50 feet away then benzene, isopropanol, and propylene oxide would be added to the list where the REL is exceeded at the fence-line.

Response: The RELs in this document are scientific health-based values. Considerations of mitigation measures requiring expenditures by industries are risk management decisions. OEHHA is not directly involved in risk management decisions. These decisions would be made at the local level and would involve the air pollution control districts.

The REL for chlorine is based on the most extensive human acute irritation study available (Anglen, 1981) and therefore contains minimal uncertainty. The hydrogen cyanide REL is based on the best animal (primate) data, since human data were not available.

Comment: All the results in Table 3 are based on a total emission rate of 6.9 grams per hour. In contrast, emergency release rates measured in hundreds of pounds per minute are common from relief valves and rupture disks. Containment or mitigation systems are often installed on the discharge lines from relief valves and rupture disks to reduce the likelihood of harm to members of the public. These containment or mitigation systems are normally designed to reduce the concentration of the chemical of concern to the Emergency Response Planning Guideline level 3 or 2 concentrations or to the OSHA IDLH concentration values. For short term accidental exposures, these levels are generally considered protective of the public health. However, the proposed RELs concentrations are often several orders of magnitude below the corresponding IDLH and ERPG level 3 values. If California EPA wishes to establish the REL values as the design levels for emergency relief containment or mitigation systems, almost all such systems will have to be rebuilt to the achieve the new lower limits.

Response: The OEHHA RELs were not developed for emergency planning purposes, but for planned releases and risk assessment, as stated in the OEHHA technical support document. The values for the severe adverse effect and life-threatening effect levels may have utility in the emergency planning/response arena. However, even in the arena of emergency planning, it is of limited applicability to the public to only consider exposure levels that are, by definition, immediately dangerous to life and health, and were developed for workers using respiratory protection (e.g., NIOSH-IDLH). Additionally, the exposure levels suggested above (NIOSH-IDLH, ERPG-3 and ERPG-2) have not gone through any independent peer review or public review process and often do not contain margins of safety. However, when these values were considered appropriate and adequately substantiated, they were adopted in the technical support document. A review of several problems associated with reliance on IDLH values for such purposes has been published (Alexeeff *et al*., 1989).

Comment: In summary, setting 1-hour acute exposure limits close to the chronic lifetime exposure limits is not based on sound science and is in direct conflict with the approach taken by ACGIH (ceiling values and short-term limits), AIHA, NIOSH and numerous international agencies. Uncertainties associated with setting acute exposure levels are different than those associated with setting chronic exposure levels and should not [be] viewed by OEHHA as identical. In addition, to the expressed scientific concerns, proposed RELs may also place undue financial burden on the California industry. In light of the above concerns, we urge OEHHA to withdraw the RELs that are proposed in the referenced documents until a more sound set of science-based guidelines are developed. We recommend that OEHHA work with the stakeholders to develop more realistic RELs which will still be protective of sensitive individuals.

Response: OEHHA is mandated by law to produce risk assessment guidelines for human health risk assessment. This document is Part I of this process. Since the other existing occupational or other non-peer or public reviewed values mentioned in the comment did not suffice when reviewed in detail, many were not used. The proximity of acute RELs to chronic values may not be surprising in cases where bioaccumulation of the chemical is minimal and acute membrane irritation is the critical endpoint. It is only appropriate to compare acute and chronic values from different sources in the context of the data upon which they are based. The single case in which the OEHHA REL is below the U.S.EPA RfC does not invalidate the REL for that chemical, nor does it discredit the document as a whole without discussion about the toxicological bases for the two values. As discussed above, the use of uncertainty factors by OEHHA is consistent with the NAS Guidelines. Therefore, there appears to be little scientific justification for retraction of these documents.

Reference:

Alexeeff GV, Lipsett MJ, Kizer KW. Problems associated with the use of Immediately Dangerous to Life and Health (IDLH) values for estimating the hazard of accidental releases. Am Ind Hyg Assoc J 1989;50(11):598-605.

Mothers of East Los Angeles / La Causa

The commentator has 4 main comments and a list of suggested changes, paraphrased and detailed below:

Comment: OEHHA, in focusing on acute toxicity exposure levels, has not taken into account the areas where individuals live, particularly in reference to communities near industrial facilities. Several high risk areas in the state are inhabited predominantly by minorities and poor people segregated by economical reasons and poverty levels.

Response: The comment points out that emissions by facilities may have differential health impacts depending on the existing toxic burden of the surrounding community. The acute toxicity reference exposure levels all contain margins of safety for individual variation of response that are intended to protect sensitive individuals, including those people with a higher existing exposure to ambient concentrations of pollutants. In addition, the facility conducting a risk assessment must add together the hazard quotients of chemicals affecting the same target organ. This accounts for some of the multiple chemical interaction that may be present. However, OEHHA recognizes that cumulative impacts from multiple facilities are not evaluated in the existing Air Toxics Hot Spots program.

Comment: Sensitive individuals, such as pregnant women, children, elderly, and persons with existing diseases are not protected with a degree of confidence by the methodology OEHHA has proposed. Specifically, an integrated approach to risk assessment which includes consideration of exposure from multiple routes (e.g., soil and water) in addition to airborne exposures, should be undertaken by state agencies.

Response: OEHHA staff have incorporated uncertainty factors to account for sensitive individuals if the data were collected from healthy subjects. In many cases, we have based these exposure levels on effects seen in sensitive individuals, such as asthmatic humans or pregnant animals. Multipathway exposures for chemicals with long environmental half-lives are considered in chronic exposure scenarios. OEHHA agrees that it would be ideal to integrate the various risks from sources other than the facility under evaluation in a cumulative risk assessment. This is not currently done in the Air Toxics Hot Spots program. This concern is particularly important when considering long-term chronic exposures.

Comment: The acute RELs do not take into account cumulative health impacts of multiple short term exposures as is the case in heavily industrialized areas in the East Los Angeles area.

Response: This is a valid point, especially when considering compounds that have cumulative toxicity. For the vast majority of cases, the cumulative impacts of multiple, short term exposures are simply not known. This is especially true when considering multiple exposures to many different chemicals such as in industrialized areas. OEHHA has attempted to use the best public health judgment possible in determining the RELs. For example, in the case of methyl bromide,

which has a cumulative toxicity to the nervous system by unknown mechanism, OEHHA considers multiple exposure data, rather than a single acute exposure, as the basis of the REL. It is not currently possible to derive RELs that consider interactions with other chemicals due to a lack of toxicological information.

Comment: The acute toxicity exposure levels should include a Level Zero, defined as the No Observable Adverse Effect Level (NOAEL) where individuals will not experience the nuisance symptoms described by OEHHA.

Response: The purpose of an REL based on a mild adverse effect is to protect against effects such as irritation of the eyes, nose or skin. These are considered adverse effects. Thus, the level I REL is a level which we believe will not result in symptoms. A substance may be detected by odor, taste or sight below the REL, but these are not considered adverse health effects unless accompanied by such symptoms as headaches, nausea, or vomiting. The NOAEL has a specific definition already and refers to the exposure level in an experiment at which no adverse health effects were observed.

Comment: Develop a Level Zero which is partly based on mortality rates of high-density areas and high-risk communities and the contribution of facilities to these problems.

Response: The REL based on a mild adverse effect (Level I) is a chemical-specific value. If the REL is not exceeded for the specified period of 1-hour, there are no anticipated health impacts from that chemical and therefore no contribution to acute mortality rates. If epidemiological data are available, they are taken into consideration when developing the REL. The REL protects against health effects much less severe than mortality.

Comment: Adopt a consistent Total Hazard Reduction Index and Total Cumulative Hazard Index so that facilities can develop risk reduction plans and procedures to mitigate acute emissions by 95%.

Response: The comment's definition of these hazard indices is not clear. Risk reduction plans and mitigation efforts can be required by local Air Districts based on current hazard index exceedances. This portion of the Air Toxics Hot Spots program is <u>not</u> within the purview of OEHHA but rather is the responsibility of the local air pollution control districts.

Comment: Develop information resources to allow residents to track indices of health impacts as environmental indicators of facilities existing in their communities.

Response: OEHHA appreciates the suggested improvements in the community right-to-know aspect of the Hot Spots Program. We agree that potential health impacts in communities should be public information. Currently, any information from health risk assessment can be obtained

from local Air Districts or OEHHA. Since the emissions of chemicals by the hundreds of facilities and respective hazards are constantly changing, the development of such a publicly available database would require considerable additional resources. We are evaluating ways to update OEHHA's risk assessment database and make it more easily accessible to the public.

Comment: Expand the list of 54 chemicals to get a more useful Hazard Index.

Response: OEHHA plans to expand the list of chemicals as soon as time, resources, and the availability of appropriate health studies allow.

National Particleboard and UF Resin Manufacturers Associations

The main points of the commentators are shown below in detail.

Comment: *The formaldehyde Level I REL should be revised.* OEHHA has used a Benchmark Dose approach to compute a 0.14 ppm Level I REL for formaldehyde with eye irritation as the toxic endpoint. The Kulle study from which the BC was derived exposed 19 subjects to various formaldehyde concentrations up to 3.0 ppm in a controlled environmental chamber for up to three hours with a number of endpoints examined.[2] There was no eye irritation at 0 and 0.5 ppm concentrations, but symptoms were noted to increase with dose at 1.0, 2.0 and 3.0 ppm.[3] The benchmark dose was derived using a log-probit analysis and a definition of BC as "the 95% lower confidence limit of the concentration expected to produce a response rate of 1%. The resulting BC of 0.25 ppm[4] was modified to 0.08 ppm through use of an uncertainty factor of 10 for intraspecies variability and a modifying factor of 0.3. That value was further modified to a one-hour exposure, resulting in a final Level I REL of 0.14 ppm.

The Kulle study data should be reinterpreted. The Associations support the use of the Kulle study; it was carefully conceived and carried out and has been widely cited in the literature. However, we believe that the Kulle data has been inappropriately characterized in the TSD due perhaps to inconsistent definitions of "mild irritation' in the OEHHA document and in the study. Responses of the subjects in Kulle to the effect that formaldehyde was perceived to be present but not annoying have been interpreted as an adverse effect by OEHHA and lumped together with the responses of annoying irritation effects in the derivation of the benchmark dose.

In the Technical Support Document, Level I is defined as follows:

This is the discomfort or mild effect level, and refers to the concentration of an airborne substance (a gas, vapor, aerosol or aerosolized particle) at or below which exposure for one hour may result in some odors, tastes and visual cues but which will cause no adverse health effects in nearly all of the population. Exposures to concentrations above this level may result in minor health effects, such as mild sensory irritation of short duration. It is the exposures above the level I REL which give rise to regulatory responsibilities under the Hot Spots program.[5] Thus, the mere detection of a substance -- the perception of formaldehyde without an unpleasant sensation -- should not trigger a Level I designation under this standard. The "mild effect level" requires more than minor, non-adverse effects.

Response: OEHHA considers mild irritation to be an adverse effect. Therefore, the mild irritation reported in the Kulle *et al*. (1987) study was included with moderate irritation for the purpose of the benchmark dose calculation.

Comment: The Associations believe that there may be a typographical error in Figure 2 on page 11 of the TSD where the following description of Level I appears:

The discomfort or mild effect level. The level at or below which no adverse effects are expected. Exposure at or <u>below</u> this level may be perceived by mild irritation of the eyes, nose or throat, or by unpleasant odors, tastes or sight... We believe that the underscored word should be "above".

Response: The comment is correct. This is a typographical error, and has been corrected.

Comment: The definition of "mild" response in Kulle is much different:

> The symptoms were scored by each subject as: none, mild (present, but not annoying), moderate (annoying), or severe (debilitating). For statistical analysis a score of 1 was assigned to none, 2 to mild, 3 to moderate, and 4 to severe.[6]

The "present but not annoying" description is directly comparable to OEHHA's description of "odors, tastes, and visual cues" which do not amount to an adverse health effect covered by Level I.

Response: The question is whether mild irritation that is "present, but not annoying" is adverse. While this is a matter of interpretation and semantics, the authors of the study clearly treat mild irritation as a distinct effect. OEHHA considers mild irritation to be an adverse health effect distinct from odors, tasks, and visual cues. Furthermore, it is clear from page 922 of the study that the mild irritation experienced by subjects included eye irritation in addition to odor detection: "...in our study at 0.5 ppm HCHO, none of our nine subjects had eye irritation, while at 1.0 ppm HCHO three of 19 reported mild eye irritation and one experienced moderate irritation." The mere detection of formaldehyde odor occurred in 4 of 9 subjects at 0.5 ppm, but this was not included in the benchmark analysis since detection of odor is not considered to be an adverse effect and no irritation was observed at that concentration.

Comment: The proper classification of the Kulle responses is critical to the development of an appropriate benchmark dose for formaldehyde. The following is a comparison of the eye irritation data points used in the model fitting and the actual base data from Kulle:

Dose	BD Data	Kulle Data	
		Present, but not annoying	Moderate
0.0	0/19	0/19	0/19
0.5	0/9	0/9	0/9
1.0	4/19 (21%)	3/19	1/19 (5%)
2.0	10/19 (53%)	6/19	4/19 (21%)
3.0	9/9 (100%)	5/9	4/9 (44%)

We ask that OEHHA rerun the model with new data points reflecting only those responses from the Kulle study coded number three to indicate annoyance.

Response: As stated above, OEHHA believes it is inappropriate to disregard mild irritation from the Kulle *et al*. (1987) study in the benchmark analysis. A benchmark analysis using OEHHA methodology (shown below), using the BD_{05} benchmark reveals that the results of the two analyses are not critically dependent on the interpretation of the mild effects in the study. The Chi-Square analysis indicates an acceptable fit for either data set, and the distance between the MLE and LCL is considerably smaller using the combined data set. The comment's recommendation would introduce greater uncertainty into the dose-response analysis.

Data set	MLE (ppm)	95% LCL (ppm)	REL (ppm)	Chi-Sq.
Mild + Moderate	0.71	0.43	**0.25**	2.81
Moderate only	1.05	0.45	**0.26**	0.11

Comment: The characterization of the Kulle results and the definition of Level I effects underscores another important consideration in the BD approach. The severity of toxic endpoints should be relevant in deciding the degree of safety factors that are appropriate.[7] It is surely more appropriate to use conservative safety margins in the various component factors of a reference exposure limit when effects such as cancer, reproductive toxicity, or other pathological changes are involved, than when endpoints such as transitory, reversible irritation are involved. This is particularly true if the "irritation" is of a minor nature. As noted in the report of the recent EPA Risk Assessment Forum on The Use of Benchmark Dose Approach in Health Risk Assessment,

> The term noncancer effect is nonspecific and encompasses a wide variety of responses, including adverse effects on specific organs or organ systems, reproductive capacity, viability and structure of developing offspring in utero, and survival...Modeling this diversity of response represents a major challenge.[8]

Response: Based on an analysis of LOAEL to NOAEL data (Fowles *et al*., 1997), we found that for certain endpoints uncertainty factors less than 10 were justified. These endpoints are mild sensory irritation and lethality. In keeping with our analysis, we have used an uncertainty factor of 3 when extrapolating from a LOAEL to a NOAEL for mild irritation or for lethality. An uncertainty factor of 3 is also used in the Benchmark Concentration approach for interspecies uncertainty if the key study is in animals and for intraspecies variability if the key study is in humans.

Comment: The issue of how to account for differences in the severity of toxicological effects is beyond the scope of these comments. It has been explored in the literature[9] and at a recent conference sponsored by the International Life Sciences Institute's Risk Science Institute.[10] We note, however, that toxicological severity is not taken into account in OEHHA's BD approach as an uncertainty factor, modifying factor, or otherwise. The relatively benign effects of low level formaldehyde exposure should be considered by OEHHA in its evaluation of the other inputs in the BD calculation which may be excessively conservative.

Response: The uncertainty factor is designed to account for interspecies uncertainty and intraspecies variability in response to a toxicant. Severity of endpoint is considered by OEHHA in the analysis by designating an effect as mild, severe, or life-threatening. Additionally, as described above, OEHHA has defined specific circumstances in which uncertainty factors less that 10 may be used (see previous response). Severity of effect is taken into consideration for some of these circumstances but is not necessarily related to the degree of uncertainty in extrapolation. While a reduced uncertainty factor of 3 is utilized when deriving a level using the benchmark concentration approach, there are no data to justify additional reductions in the total uncertainty factor based on effect severity.

Comment: The Benchmark Dose is defined as the 95% lower confidence limit of the concentration expected to produce one response for every 100 subjects exposed at this dose. The BD method assumes a log-probit concentration versus response relationship to identify the concentration expected to produce 1% increase in toxic response (TC01) via a maximum likelihood estimate. The incremental increase in risk over background is often termed the Benchmark Response ("BMR"). OEHHA itself has noted, "[f]or a toxic response with a specific threshold, 1 percent approaches the margin of useful extrapolation for acute noncarcinogenic data due to the limited number of animals used in most experiments." (TSD p. 24). Study size is even more problematic under the 1% BMR in human studies because of typically limited participation. The Associations urge OEHHA to use a 5% or 10% BMR in its benchmark dose calculation. Although the EPA Report suggests the use of BMRs between 1% and 10%, it raised a number of cautions about this selection:

> ...the BMR should be selected near the low end of the range of increased risks that can be detected in a bioassay of typical size. Comparison of the BMD with the NOAEL for a large number of developmental toxicity data sets indicated a BMR in the range of 5 to 10 percent resulted in a BMD that was on average similar to the NOAEL (Allen *et al*., 1994a; Faustman *et al*., 1994).

One cannot detect increased risks in the Kulle study doses at the 1% level or anywhere near it. The LOAEL is at 1.0 ppm; the NOAEL is at 0.5 ppm and the indicated BD is 0.25 ppm. The EPA Report also noted the importance of model independence and the fact that various dose response models can fit experimental data well, but "produce widely divergent estimates of risk at doses far below the range that produce measurable increases in response (Crump 1985).''[11] EPA cautions that for the BD approach to be relatively model independent, the BMR cannot be much smaller than increased responses that can be measured reliably in experimental groups of typical size.". Clearly, the 19 subjects in the Kulle study are far fewer than the 100 or more subjects that are mentioned in the EPA Report as a typical minimum for a 1% BMR. A Workshop convened by the International Life Sciences Institute (the "ILSI Workshop'')[12] took a more decisive stand on this issue. The Workshop participants "...generally agreed that selecting an effective dose (ED) for BMD calculation at the ED01 (01=1% above the experimental background rate or control) was too low...It was acknowledged that use of either an ED_{05} or an ED_{10} for BMD calculation was appropriate, recognizing that future research might show the advisability of selecting one value over the other (Faustman *et al* 1994).[13]

Response: OEHHA agrees that for the sake of consistency with the consensus reached at the above workshops, the BC_{01} should be changed to BC_{05}. This change will be made in the technical support document for the benchmark calculations, including formaldehyde. However, OEHHA notes that the justification for the BC_{05} in the USEPA report is based on comparison with NOAELs and uses only developmental toxicity data for such comparisons. Future empirical analyses of acute data sets other than developmental toxicity may necessitate reevaluating the use of the BC_{05} benchmark.

We wish to emphasize that the analysis presented by Crump and cited in the benchmark dose workshop is limited only to developmental endpoints. An analysis of the effects of changing the benchmark dose calculations in the technical support document from the 1% to the 5% response rate indicates that endpoints other than developmental toxicity (CNS, irritation, and lethality) all yield very similar values for either the 1% or 5% response rates. The magnitude of difference is on average only a factor of about 1.3.

Comment: OEHHA justifies its use of the 1% measure by the fact that it is consistent with its intent to protect "essentially all" individuals from the acute toxic endpoints. There are several concerns with this argument. First, as noted above, mathematically stretching down to a lower BMR impairs the scientific integrity of the result. The issue is not whether a data set can be manipulated to reach the level where the incremental 1% over background is covered, but rather whether there is scientific support for that approach. Moreover, the interest in providing protection to the broad array of the population is addressed in at least three other ways in the REL calculations. A study conducted last year by Allen *et al*.[14] reviewed the relation between benchmark doses and NOAELs for over 400 developmental toxicity experiments. The Benchmark doses --which had been determined using the Weibull model, a 1% BMR and 95% lower confidence limits -- were, on average, 30-fold lower than the comparable NOAELs.[15] We presume that similar results would be obtained if the data were analyzed with the log-probit model used by OEHHA. This suggests that the change in methodology, in and of itself, is introducing a 30 fold reduction in the indicated levels. While changes of this magnitude for individual substances may be justified based on improved information, we know of no scientific justification for an average reduction of this size. The combination of conservative assumptions including the 1% BMR are driving the changes. The Associations urge OEHHA to recalculate the formaldehyde Level I REL (and RELs for other chemicals, where appropriate) based either on a 5% or 10% BMR.

Response: As discussed in the response to the Chemical Manufacturers' Association, OEHHA is changing the benchmark dose methodology from a 1% response to 5%, in accordance with the opinions of the Benchmark Dose Workshop. However, there are several issues raised in the comment in support of this change that should be addressed. First, the "stretching down" of the benchmark response to a 1% response rate is much less influential on the REL than the comment implies, and is only a factor of about 1.3 below an REL based on the 5% response, as discussed above. The data sets analyzed by Allen (1994) contained only developmental defects and may not adequately represent the dose-response slopes or experimental designs of many other acute

toxicological responses. In addition, it is inappropriate to judge the benchmark dose solely on its proximity to the NOAEL, since it is clear that the benchmark dose is a methodological improvement over the NOAEL approach. Many data sets do not even establish a NOAEL, but are still useful for benchmark calculations. Finally, the uncertainty factors used in conjunction with the benchmark dose calculations have been reduced by 3.3-fold compared to the NOAEL approach since we believe that some degree of variation in establishing a dose-response threshold has been accounted for by use of the 95% lower bound on the experimental dose-response. OEHHA is therefore reducing uncertainty by use of benchmark dose calculations and is using correspondingly less conservatism in deriving RELs.

Comment: The Associations acknowledge that statistical Lower Confidence Limits ("LCL") have typically been used in expressing benchmark doses rather than maximum likelihood estimates. OEHHA has selected the 95% Lower Confidence Limit expression in its BD calculations including that for formaldehyde. Although the 95% level is not an uncommon confidence interval, selections often range from 90% to 99%. The choice of 95% is a policy decision. Some traditionally noted benefits of confidence limits include their sensitivity to the sample size, their stability in the face of minor changes in the data, and their ability to be determined in some instances when the MLE cannot be. However, like all of the other factors that go into the BC calculation, the appropriateness of the 95% lower confidence limits must be evaluated against the backdrop of the other assumptions that have been made and the scientific knowledge about the substance. If the combination of conservative assumptions leads to results that are out of the range of practical experience, then one must evaluate the justification for the assumptions.

It is undeniable that the calculation of the BC depends heavily on the BMR as well as the size of the statistical confidence bound that is used. The selection of a 1% BMR in the case of formaldehyde as opposed to 5% or 10%, not only drives down the MLE curve but also causes even larger disparities between the MLE expression and the 95% LCL value than occurs at the higher level. The poorer the quality of the data used, the lower the statistical confidence particularly at the lower portions of the curve. The relatively small group sizes employed in most noncancer toxicology studies will also necessarily impart a substantial degree of conservatism to lower bound benchmark dose estimates. Standard carcinogenicity bioassay designs call for 50 animals per sex per treatment group. Human studies for non-cancer endpoints, and particularly endpoints of relatively minor toxic severity are typically much smaller. The Kulle study with 19 participants is not atypical. Although the use of a human study eliminates the use of the default interspecies uncertainty factor of 10, it almost guarantees a penalty through the inflation towards zero of the lower confidence limit. The Associations urge OEHHA to include in the revised TSD a graphic representation of the benchmark dose derivation similar to what has been provided for most other chemicals subject to the benchmark dose approach. This will allow both regulators and the public to better understand the differences between the MLE and the LCL expressions.[16]

Response: OEHHA will provide the graphic display of the formaldehyde benchmark dose to be consistent with the graphic displays already contained in the document for other chemicals, as requested. The use of the lower 95% confidence limit has wide precedent in statistical analyses as well as benchmark dose calculations (Auton, 1994; Malsch *et al*., 1994; Crump, 1984).

Furthermore, as discussed in a previous comment, the magnitude of change between the BC_{01} and the BC_{05}, including the 95% lower bounds, is only about 1.3 on average. Therefore, the 95% lower bounds do not diverge at an excessive rate in this region. This can be seen in the graphic displays of the benchmark calculations for ammonia, carbon tetrachloride, several of the glycol ethers, and many other chemicals in the technical support document. In general, the minimal distance between the MLE and the confidence bound occurs at the 50% response rate, which is obviously far in excess of an acceptable response rate. As the response rate deviates from that point, the distance between the MLE and confidence bound increases. There is no *a priori* reason for selecting 5% over 1% response based on distance between confidence bound and MLE. Empirically, the data sets in this document do not show a large deviation from 95% lower bounds of 1% vs. 5% response rates in either Probit or Weibull models.

Comment: Additionally, it would be helpful to have more detail on the computer program that has been employed in the formaldehyde analysis. The TSD references a 1983 unpublished work by Crump -- "Probit-A Computer Program to Extrapolate Quantile Animal Toxicological Data to Low Doses" -- as the program that was used to fit the human data from Kulle. The assumptions that are used in any program are critical to understanding the appropriateness of its use. The process should be totally transparent.

Response: OEHHA will provide the mathematical basis for the calculation of the benchmark dose in the Technical Support Document.

Comment: The Level I REL for formaldehyde uses an uncertainty factor ("UF") of 10 to account for "individual variation." An additional modifying factor of 0.3 was used because "...the BC accounts for some degree of individual variation. The Associations submit that either the uncertainty factor should be lowered or a reduction should be made in the modifying factor -- perhaps to 0.15 or 0.2 rather than the 0.3 that has been used.

Response: The suggested change is not justified by the commentator. The Kulle *et al*. (1987) study only examined up to 19 healthy subjects. These subjects do not represent the most sensitive individuals in the entire population. The actual range in sensitivity in the general population is likely to be greater than 1.5 or 2-fold.

OEHHA has changed its uncertainty factor methodology since the release of the public comment draft. The interspecies uncertainty factor for formaldehyde is now 3. A modifying factor is no longer applied. This reflects OEHHA's use of UFs with the BC approach.

Comment: As noted by the National Academy of Sciences in its report, "Science and Judgment in Risk Assessment:"

> When reporting estimates of risk to decision-makers and the public, EPA should report not only point estimates of risk but also the sources and magnitudes of uncertainty associated with these estimates. p. 12-19.

Response: The estimates and uncertainty factors for each chemical are specifically given in the Technical Support Document. Statistical uncertainties in exposure estimates are addressed in a separate guideline document, *Technical Support Document for Exposure Assessment and Stochastic Analysis.*

Comment: The rationale for the uncertainty factor, intraspecies variability, is expressly addressed by other aspects of the BMD:

> Furthermore, the TC01 [1% BMR] is consistent with the definition of the proportion of the population that may not be protected by these levels (as defined previously, these levels are intended to protect "essentially all" individuals and a very small proportion may not be protected). Use of the 95 percent lower confidence limit on concentration takes into account the variability of the test population .... TSD, page 24.

The interrelation of the uncertainty factors with other components of the BD has been repeatedly noted by experts in the field. For instance, some at the ILSI Workshop questioned the use of LCL in light of the adjustments that are typically made elsewhere in the BD calculation:

> The use of the uncertainty factor for intraspecies variability elicited a discussion on the significance of using the central estimate versus the lower confidence limit (LCL) of the BMD. Some participants suggested that the LCL accounts for intraspecies variability as well as experimental variability. (ILSI Workshop Report, p. 11)

Response: It is true that the relationship between the 95% LCL and intraspecies variation was mentioned in the proceedings; however, the workshop ultimately decided <u>not</u> to recommend any changes to the intraspecies uncertainty factors. OEHHA reduced the intraspecies uncertainty factor to 3 when using a BC approach on a study in normal human subjects since we believe that some degree of individual variation in the test population was accounted for by use of the 95% LCL.

Comment: The EPA Report noted the extensive work that is being done on uncertainty factors[17] and highlighted other items that should influence their determination:

> ...the calculation of the BMD depends on the BMR as well as the size of the statistical confidence bound employed. These additional considerations may need to be accounted for when selecting uncertainty factors for BMDs.

The EPA also noted that, "Some biological considerations (e.g., relating to the possibility of a threshold for the responses under investigation) could affect the selection of uncertainty factors." This is particularly apt in the formaldehyde setting where it is agreed that there is a threshold for acute effects of formaldehyde.[18]

Response: OEHHA continues to believe that a threshold exists for the onset of non-cancer health effects, including those caused by formaldehyde. Both the NOAEL and benchmark dose approaches yield results consistent with a practical threshold.

Comment: Another biological consideration of even greater import, as noted above, is the severity of the toxicological endpoint. This is particularly relevant to formaldehyde. When the debate over toxicity turns on whether a substance merely can be detected or whether it is minimally annoying, the uncertainty factors should be viewed in a different light than when effects such as reproductive toxicity or other endpoints are at issue.

Response: The severity of effect is accounted for by the use of severity effect levels and also by OEHHA's use of uncertainty factors. We agree that minimal irritation should be viewed differently than reproductive effects. For this reason, mild irritation is considered a mild adverse effect and reproductive or developmental toxicity is considered a severe adverse effect. The mere detection of a compound, in absence of toxicological signs or irritating or annoying symptoms, is not considered by OEHHA as a mild adverse effect. In addition, OEHHA has reduced the LOAEL to NOAEL uncertainty factor to 3 for mild irritation.

Comment: Again, one can address the overall uncertainty of the BMD calculation in the UF factor, in the modifying factor, in the use of a different BMR, in the use of the MLE versus the LCL, or in a combination of ways. The factors are interrelated. The Associations submit that the underlying data and overwhelming body of knowledge on formaldehyde[19] justify either the elimination of the uncertainty factor or further reduction of the modifying factor to 0.1 or 0.2.

> *19/ Appendix E of the TSD lists chemicals for which complete data base searches have been completed, those for which searches are in progress, and those which are to commence in 1995. Formaldehyde does not appear on any of the lists. The literature on formaldehyde health effects is extensive.*

Response: OEHHA has agreed to change the BC_{01} to BC_{05} in accordance with the recent workshop by ILSI and reported in the literature (Regul. Toxicol. Pharmacol. 21:296-306, 1995). The UF methodology for the BC approach has been changed. A factor of 3 is used for the interspecies or intraspecies uncertainty factor, depending on whether the key study was performed in humans or animals. The modifying factor is no longer used.

In regard to footnote #19, a literature search has been completed for formaldehyde. Unfortunately, Appendix E incorrectly indicated that the literature search was not yet completed.

Comment: The Hot Spots program requires the facility to evaluate potential risk to the surrounding population in ways that add still additional safety factors. These features, in effect even if not directly, lower the toxicity exposure levels even more.

For example, the facility must create an exposure assessment to determine the ground level concentration at each gridded receptor and the expected exposure to specific, sensitive receptors. Concepts of "maximum impacted offsite locations," "maximum exposed individual residents," and "maximum exposed individual workers" are woven into this exercise. The probability that the maximum exposed individual would be a person whose sensitivity would only be reflected by the 1% BMR is extremely small.

Response: The RELs are used to evaluate impacts of many receptors, not just the maximum impacted receptors (MEIs) as indicated by the comment. The MEI exposures may also be experienced by a large number of people in a given gridded receptor. By protecting the most sensitive receptor, RELs offer protection to the majority of individuals in an exposure area. In accordance with earlier comments, the BC_{01} will be changed to BC_{05}.

Comment: Second, added responsibilities to prepare a detailed isopleth map arise if the Hazard Index for any endpoint exceeds 0.5. The net effect of this provision is to reduce by a factor of 2 the computed RELs, in spite of the fact that they already reflect the numerous other conservative assumptions and safety factors described above. Although these various safety factors ---1% BMR, use of 95% LCL, uncertainty factors, no accommodation to severity of toxicological endpoint, maximum exposed individual, and 0.5 HI trigger for mapping -- may be logical and defensible when analyzed individually, they have a multiplicative impact when incorporated into the Hot Spots Program together. The result is an overly-protective and burdensome regulation.[20]

20/ OEHHA suggests that it is required by statute to employ a margin of safety. Although there is a question as to whether the provisions of AB 1807 and 2728 apply to the Hot Spots program; in any event, this language should not be used repetitively to make the risk assessment scientifically meaningless.

Response: OEHHA has withdrawn the proposed requirement regarding the HI of 0.5. The other comments have been addressed in detail above. The commentator's footnote (#20) is in error; Health and Safety Code Section 39660 (Ch 1161, Sec 4) states specifically to use "...an ample margin of safety which accounts for variable effects..."

Comment: The Associations ask that the data from the Kulle study be recharacterized and that appropriate changes in the modifying factors or elsewhere be made to remove the layering of safety factors.

Response: This concern has been addressed in the calculations above. Recharacterizing the data from the Kulle *et al*. study results in only a minute change in the REL. The current approach is consistent with OEHHA's definition of adverse effects.

Comment: OEHHA has set a Level II exposure for formaldehyde of 10 ppm for "disability or serious effect[s]" based on the AIHA-ERPG-2. However, in the TSD the following description is given for expected effects: "Moderate eye irritation and lacrimation may be experienced with exposure to formaldehyde above this level." The Associations recommend that this description be modified by removing the word "moderate" and changing "may" to a more forceful statement. Exposure to formaldehyde at these levels would be very noticeable and very uncomfortable to almost all individuals.

Response: The level II for formaldehyde has been revised. It is now based on decrements in FEV_1 in exercising asthmatics. The level II was revised to 1.6 ppm

Comment: OEHHA has proposed the following RELs for methanol:

Level I Discomfort	2.1 ppm (2.8 mg/m^3)
Level II Disability or Severe Effect	5.1 ppm (6.6 mg/m^3)
Level III Lethality	40.0 ppm (52.4 mg/m^3)

This substance, perhaps more than any other chemical in the Evaluation, reflects the difficulties that are encountered when assumptions are applied without reference to the practical implications of the end result. The Occupational Safety & Health Association's Permissible Exposure Limits (''PEL'')[21] and American Conference of Governmental Industrial Hygienists ("ACGIH") Threshold Limit Value ("TLV")[22] for methanol are 200 ppm (262 mg/m3) on an 8-hour time-weighted average basis. These levels, promulgated by two prestigious organizations charged with the protection of worker health are five times higher than the level that OEHHA has alleged "may result in death due to respiratory or cardiac arrest."

Response: The 3 levels for methanol are addressed individually in the following comments and responses.

Comment: The Level I REL For methanol should be changed. The Level I REL is based on a study of 12 healthy young men exposed to methanol at 250 mg/m^3 for 75 minutes in controlled chambers (Cook *et al*. 1992)[23]. Note that this is below the OSHA and ACGIH levels in both concentration and time of exposure. A battery of neurobehavioral challenges was evaluated for methanol-induced changes. OEHHA made the assumption that 250 mg/m^3 (190 ppm) was the LOAEL; it then applied a 100-fold safety factor (10-fold for LOAEL -> NOAEL; 10-fold for interspecies [sic] differences, and extrapolated from the 75-minute exposure of the study to a 60 minute acute exposure using the following relationship $C^n * T = K$, where n=2, to derive a REL Level I of 2.8 mg/m^3 (2.1 ppm). This is a poor choice of study and endpoint. Furthermore, OEHHA differs with the authors of the study in the interpretation of results. For example, a very small number of subjects (n = 12) was followed. Further, of 20 commonly used tests of sensory, behavioral, and reasoning performance before, during, and after each exposure, no detectable effect on the subjects' performance was noted, except in "subjective ratings of fatigue" (Cook *et*

al. 1992) and the timing of peaks of brain wave patterns in response to light flashes and sounds, that varied by latency of response. Marginally significant effects were found for subjective levels of concentration and performance on the Sternberg memory task, which although statistically significant, were not outside the range of values observed with the subjects in sham exposures. Therefore, the findings were not clinically relevant. When considered as a whole, there is a lack of internal consistency of response. For example, reported reductions in concentration and increased subjective feelings of fatigue should also be reflected in performance on all of the neurobehavioral tests. Also, reduction in reaction time on the Sternberg memory test should be mirrored by a slower reaction time in the Symbol Digit substitution task. Similar changes in other measures of brain wave patterns should have been observed in addition to the changes in latency of response to light flashes and sounds. The authors of the Cook study indicate clearly in their conclusions: "Given the plausible role of chance in obtaining positive results in this study, and the uncertain significance of changes in the event-related potentials, it is inappropriate to conclude that these positive effects are attributed to methanol exposure". There are other significant shortcomings in the derivation and explanation of the REL. First, the 10-fold safety factor for estimating a NOAEL based on the LOAEL is inappropriate. Even if one accepts the noted changes as adverse effects, a safety factor of 10 is unnecessarily conservative given the mild (benign) nature of the response. Second, a 10-fold safety factor could be employed to account for inter-individual, or intraspecies extrapolation, but the reference to interspecies is misplaced. The 10-fold safety factor for individuals is a standard default assumption. Third, no consideration was given to mechanism of action, and/or ultimate toxic metabolite.

Response: OEHHA concludes that the Cook *et al*. (1991) study is adequate for setting the mild adverse effect level REL. It is a well-conducted study of neurobehavioral effects due to methanol. Its faults are the small sample size and failure to test at greater concentrations. The Cook *et al*. (1991) study showed statistically significant CNS effects in methanol-exposed individuals compared to controls. The comment argues that these effects (fatigue and visual evoked potential) are not biologically significant and are inconsistent with the other neurological tests. However, it is well-known that methanol causes acute CNS depressant effects (Andrews and Snyder, 1991; Kavet and Nauss, 1990). The statistically significant effects reported in Cook *et al*. (1991) can therefore be interpreted as consistent with the onset of CNS effects. The apparent discrepancies between the positive Sternberg test and the negative Symbol Digit substitution test highlighted by the comment are not pertinent, since the Sternberg test results were not statistically significant. The authors of the study were tentative in concluding definite effects from methanol exposure. We continue to believe that the statistically significant effects and other trends observed in the paper were consistent with the hypothesis that methanol exposure causes CNS depression and that these effects warrant concern. However, because of the uncertain significance of the findings of this study as a whole, OEHHA will consider this study to represent a free-standing NOAEL until further research is available. An uncertainty factor of 10 for intraindividual variability will be applied, as will time extrapolation, yielding a REL of 21 ppm (1.7 mg/m^3).

Comment: The Level II REL for disability is similarly inappropriate given the other reference standards. The Level II REL is based on a NOAEL of 1,300 mg/m^3 (1,000 ppm) for congenital

malformations in mice exposed to methanol for 7 hours/day on gestation days 6-15 (Rogers *et al*. 1993).[24] The LOAEL was 2,600 mg/m3 (1,200 ppm), at which an increase was seen in the number of fetuses per litter with cervical ribs (small ossification sites lateral to the 7th cervical vertebra). The next higher effect level was 6,500 mg/m3 (5,000 ppm), for which increased incidences of exencephaly and cleft palate were reported. For 1% and 5% added risk, the study authors calculated maximum likelihood estimates, and lower 95% confidence bound benchmark doses which were adopted by the state of California (see Table 1). A 30-fold safety factor was applied by the OEHHA (100-fold for inter- and intra-species variability, and an additional modifying factor of 0.3 "since the BC approach accounts for some degree of individual variation". The 7-hour value was extrapolated to a 1-hour REL using the formula $C^n * T = K$, where n=2, with a resulting Level II REL of 6.6 mg/m^3 (5.1 ppm). The OEHHA recommends that this REL be revised when a primate reproductive study is available.

Table 1. Exposures Corresponding to Incremental Risk of Cervical Rib Incidence in Methanol-Treated Mice(mg/m^3)

	1% added risk		5% added risk	
	MLE	BD_{01}	MLE	BD_{05}
Rogers *et al.*	302	58	824	305

The Rogers *et al*. report is the best study available in the peer-reviewed literature for setting a reproductive toxicity-derived safe exposure level. This study was well conducted and well-controlled. However, one limitation is the fact that it was performed in a non-primate species. Point (MLE) and lower-bound (BMD) benchmark dose estimates from this data set appear to be reasonable. OEHHA's application of safety/uncertainty factors is not inconsistent with their traditional conservative assumptions. However, in spite of the consistency of approach with normal default assumptions, one must grapple with the paradoxical nature of the 5.1 ppm resulting value for reproductive or developmental toxicity in light of the 200 ppm OSHA and ACGIH values. There is no indication whatsoever that the OSHA and ACGIH levels are inadequate or inappropriate. In the face of these disparities, the Associations submit that reliance on generic uncertainty factors is misplaced. One possible explanation for the problem arises from the study. There is concern that mice are not an appropriate species for human health risk assessment due to the high-dose sensitivity of rodents that is observed and predicted by pharmacokinetics of methanol disposition. A primate study would be preferred because of the potential interspecies differences in methanol metabolism. Although not yet published in the peer-reviewed literature, such a study exists, and has been cited by the World Health Organization (1994)[25] and Kavet and Nauss (1990)[26]. These two groups report that the Japanese Institute for Applied Energy, with the sponsorship of the New Energy Development Organization (NEDO), conducted an extensive research program in which rodents and cynomolgus monkeys were

exposed to 13, 130, and 1,300 mg/m^3 (10, 100, and 1,000 ppm, respectively) of methanol for up to 30 months. Summaries of the studies indicate that no reproductive (or other toxic or carcinogenic effects) were evident at levels of 130 mg/m^3, and no teratogenic effects were observed even at 1,300 mg/m^3.

Response: OEHHA thanks the commentator for bringing the Japanese Institute for Applied Energy/New Energy Development Organization data to our attention. It appears that this is a chronic study (30 months), which is inappropriate for use as the basis for an acute, severe adverse effect value. The information presented by the comment is too general and vague to allow thorough evaluation of these data (e.g., no sample size or dose-response information is presented).

The severe adverse effect level for methanol is lower than occupational standards as described by the comment. However, the Rogers *et al*. (1993) study in mice is more recent than the most recent versions of the ACGIH-TLV (1992), which only describe congenital malformations in rats at high doses of methanol from Nelson *et al*. (1985). It is possible that, given the new developmental toxicity information, the ACGIH-TLV committee will revise the TLV.

Even if this was not the case, using workplace standards to set acceptable community standards is inappropriate. The occupational standards developed by the ACGIH are clearly intended for purposes other than community health-based values. Even ACGIH acknowledges the limitation of the TLV's utility in the second paragraph of the Introduction section of the TLV document: *"These values are intended for use in the practice of industrial hygiene as guidelines or recommendations in the control of potential health hazards and for no other use, e.g., in the evaluation or control of community air pollution or physical agent nuisances...These values are not intended as fine lines between safe and dangerous exposure concentrations...."* The TLVs are designed to protect healthy workers and not the infirm, infants, children, pregnant women, or elderly. Thus, the TLVs and RELs cannot be directly compared.

The severe adverse effect level for methanol has been recalculated using the BD_{05} and this is reflected in the Technical Support Document. The level II REL thus changes from 6.6 to 35 mg/m^3. We reiterate that a severe adverse effect level based on reproductive effects will be revised upon publication of a primate study.

Comment: A Level III (lethality) REL that is five times lower than accepted occupational standards is inappropriate. OEHHA's life threatening effect level REL is based on a 1931 study of rhesus monkeys, rabbits, and rats, in which animals were exposed to 1,300 mg/m^3 - 52,400 mg/m^3 (1,000 - 40,000 ppm) for 1-18 hours per day for up to 4 days. The point selected by OEHHA for derivation of its Level III REL was the LOAEL of 40,000 ppm for 1 hour, "the concentration which resulted in death in all animals several days following exposure." It is not clear from the description of the study in the TSD which animals succumbed, but it appears that monkeys were most likely the target species. To the LOAEL of 40,000 ppm (52,400 mg/m^3), a 1,000-fold uncertainty factor was applied: 10-fold for LOAEL-> NOAEL; and 100-fold for inter- and intra-species adjustments. No time adjustment was applied, as the exposure duration was one

hour. The resulting Level III REL was 40 ppm or 52.4 mg/m^3. It is unclear why this particular study was selected; there is a large body of literature, some it of quite recent (reviewed in Kavet and Nauss, 1990; WHO, 1994) on both acute and chronic effects of methanol intoxication. One of the conclusions that continues to surface in the literature is that route of exposure is critical factor for methanol toxicity. Rather, the intake dose and resulting blood methanol concentrations are critical to methanol's toxicity (Clayton and Clayton, 1982)[27]. Thus, oral exposures to methanol in appropriate species could be employed in developing more reliable estimates of exposure levels protective against acute lethal toxicity. Whatever the strengths or weaknesses of the methodology used, a comparison of OEHHA's Level III REL for lethality (52.4 mg/m^3) to the OSHA PEL or ACGIH TLV of 262 mg/m^3 for an 8-hour time-weighted average indicates the inappropriateness and unacceptability of the new level.

Response: If inhalation data are available, these are preferred over data from other routes of exposure for setting inhalation RELs. The RAAC recommended that route-to-route extrapolation not be performed for acute REL development. The "large body of literature" mentioned in the comment contains little, if any, inhalation data, and although the review by Kavet and Nauss (1990) is fairly recent, the information reviewed in their paper is not. However, OEHHA agrees that the life-threatening effect level for methanol appears to overestimate lethal effects. The revised NIOSH 1996 IDLH level of 6,000 ppm (7860 mg/m^3) has been proposed as the life threatening level for methanol by OEHHA.

Comment: The Associations respectfully request that OEHHA reexamine the RELs that have been proposed for methanol in light of the evaluations of other governmental and private health agencies. Attached as Exhibit D for the Agency's consideration is a "Determination of Alternative Safe Human Exposure Levels for Discomfort, Disability, and Lethality" prepared by Drs. Thomas Starr and Larisa Rudenko of Environ.

Response: OEHHA appreciates the efforts to improve the technical support document. We have reviewed the attachments provided. As noted in our previous response to this commentator, we have revised all three toxicity criteria, including the level I REL.

Comment: Attached as Exhibit E is a description of some concerns raised by Environ regarding the use of additivity when compiling the hazard index from various hazard quotients. Even if the same endpoint is being evaluated, it is not always appropriate to aggregate these quotients.

Response: There are very little data available on effects of chemical mixtures. When two or more toxicants evaluated in a risk assessment impact the same target organ or system, it is prudent to assume additivity. There are a limited number of examples of both synergism and antagonism in the literature. However, in general, these type of data are lacking. The large number of possible combinations of chemicals to which people are exposed simultaneously both from the facility being evaluated as well as other sources cannot be adequately characterized by the available data. If a risk assessor has data pertaining to the specific mixture being evaluated, that data can be supplied with the risk assessment as supplemental information. However, it is not

possible to ascertain the combined effects of exposure to emittents from a hot spots facility and exposure to other airborne, water-borne, food-borne or medicinal chemicals to which an individual is also simultaneously exposed. In addition, the physiological status of an individual including such factors as age, health, pregnancy status, lactational status, and nutritional status will likely impact the response to exposure to multiple chemicals. This is not adequately reflected in the available data on chemical mixtures. Assuming additivity is one way to account for the large amount of uncertainty. It is not particularly health-protective in some instances where synergism has been demonstrated.

References cited by the commentator:

2/ Kulle, J.T., L.R. Sauder, J. R. Hebel, D. Green, and M.D. Chatham 1987. formaldehyde dose-response in healthy nonsmokers. J. Air Pollution Control Assoc. 37:919-924, at 920, Col 2. A copy of the Kulle study is attached as Exhibit C. 3 Id. at 921.

3/ Id. at 921.

6/ Kulle at 920.

7/ Dourson, M.; Stara, J. (1983) Regulatory history and experimental support for uncertainty (safety) factors. Reg. Toxicol. Pharmacol. 3: 224-238.

8/ EPA, The Use of the Benchmark Dose Approach in Health Risk Assessment. (1995) EPA/630/R-94-007 (the “EPA Report”).

9/ See DeRosa, C.T., Stara, J., and Durkin, P. (1985). Ranking chemicals based on toxicity data. Tox. Ind. Hlth. 1:177-199.

10/ International Life Sciences Institute and Risk Science Institute, Report of the Benchmark Dose Workshop, September 28-30, 1993. (“ILSI Report”).

11/ Id.

12/ See footnote 10, supra.

13/ ILSI Report, at page 8.

14/ Allen, B.C.; Kavlock, R.J.; Kimmel, C.A.; Faustman, E.M. (1994) Dose-response assessment for developmental toxicity: II. Comparison of generic benchmark dose estimates with NOAELs. Fund. Appl. Toxicol. 23: 487-495.

l7/ Hattis, D.; Lewis, S. (1992) Reducing uncertainty with adjustment factors. The Toxicologist. 12: 1327. (EPA Report at 50).

21/ 29 CFR ¤ 1910.1000, Table Z-1.

22/ American Conference of Governmental Industrial Hygienists, “Threshold Limit Values and Biological Exposure Indices for 1994-1995,” p.25.

23/ Cook, M.R.; Bergman, F.J.; Cohen, H.D.; Gerkovich, M.M.; Graham, C.; Harris, R.K.; and Siemann, L.G. 1991. Effects of methanol vapor on human neurobehavioral measures. Health Effect Institute, Research Report No. 42.

24/ J Rogers, J.M.; Mole, M.L.; Chernoff, N.; Barbee, B.D.; Turner, C.I.; Logsdon, T.R.; and Kavlock, R.J. 1993. The developmental toxicity of inhaled methanol in the CD-1 mouse, with quantitative dose-response modeling for estimation of benchmark doses. Teratology. 47: 175-188.

25/ World Health Organization, the United Nations Environmental Program, and the International Labor Organization. 1994. International Program on Chemical Safety: Environmental Health Criteria - Methanol. Draft Report. Geneva, Switzerland.

26/ Kavet, R. and Knauss [sic], K.M. 1990. The toxicology of inhaled methanol vapors. Critical Reviews in Toxicology 21(1):22-50.

27/ Clayton, G.C. and Clayton, F.E., eds. (1982) Patty’s Industrial Hygiene and Toxicology: Volume 2C: Toxicology with cumulative index for vol. 2. 3rd Edition. John Wiley & Sons. New York, pp. 4527-4551.

Additional References:

Auton, T.R. 1994. Calculation of benchmark doses from teratology data. Reg. Toxicol. Pharmacol. 19:152-167.

Crump, K.S. 1984. A new method for determining allowable daily intakes. Fundam Appl. Toxicol. 4:854-871.

Malsch, P.A., Proctor, D.M., and Finley, B.L. 1994. Estimation of a chromium inhalation reference concentration using the benchmark dose method: a case study. Reg. Toxicol. Pharmacol. 20:58-82.

Pacific Gas and Electric Company

Comment: (1) The guidelines should allow risk managers to deviate from the OEHHA recommendations relative to the factor of safety below the lowest observed adverse effects level.

(2) Evaluations should not be required where RELs are not provided, but a comparison to the LOAEL should be added.

(3) It is more informative to calculate a facility's maximum potential hourly impact, and compare that to the maximum measured hourly background, than to add the maximum potential hourly impact to the average annual background. Nevertheless, districts should be allowed to determine whether such comparisons are beneficial.

(4) Proposed factors of safety used for each degree of uncertainty should relate to the severity of the effect. If a factor of safety of ten/degree is appropriate for lethal effects, a factor of safety closer to two/degree would be more appropriate for irritation.

The Office of Environmental Health Hazard Assessment (OEHHA) proposes on pages 21-22 of its January 1995 draft "The Determination of Acute Toxicity Exposure Levels for Airborne Toxicants" using factors of safety of ten for each successive area of uncertainty. Specifically one factor of ten is always imposed, and additional factors of safety (which OEHHA refers to as an "uncertainty factor") of ten is proposed whenever the effects data is based on: LOAEL, animal data, average persons, or deficient studies instead of NOAEL, human data, most sensitive persons, well designed studies.

Because these factors are then multiplied together, the combined factor of safety applied can be as high as 10^5 or 100,000 regardless of how insignificant the effect might be, or as low as 10 regardless of how serious the effect might be, depending entirely upon the nature of the data, not upon the nature of the effect. Since circumstances which cause more serious effects are generally better documented, this policy tends to result in the least protection against most serious, certain and common effects. For example, with respect to acrolein OEHHA proposes a factor of safety of about 5 relative to "may be lethal" effects, but a factor of safety of 1,000 relative to "may result in irritation" effects. That should be reversed!

Response: There are several inaccuracies in the comment's statements. First, OEHHA does not use uncertainty factors for "well designed studies" or data gaps in the acute document. Second, the application of uncertainty factors by OEHHA is to account for specific sources of uncertainty and variability not addressed in the scientific literature: individual variation, interspecies differences, and estimation of a NOAEL from a LOAEL. The maximum combined uncertainty factor is 1000, used when deriving an REL from an animal study without a reported NOAEL. The minimum uncertainty factor is 1, as in the case of sulfuric acid, where the REL is based on a study in a human sensitive population (asthmatics). OEHHA accounts for severity of effects in two ways: (1) by categorizing them into one of three levels: mild adverse effect level, severe adverse effect level , and life-threatening effect level; and (2) by using smaller uncertainty factors in predetermined situations. RELs based on LOAELs for mild sensory irritation have smaller

uncertainty factors of 3 instead of the traditional 10. OEHHA has incorporated the best available scientific information into the traditional uncertainty factor method where data have allowed such a departure to occur without endangering community health. By applying consistent uncertainty factors for each level, the risk manager is provided with as much information as needed to understand the potential health effects at varying concentrations.

The uncertainty factor used by OEHHA for acrolein is 100, not 1000 as stated in the comment.

Comment: In proposing large added factors of safety for each added degree of uncertainty, OEHHA creates an obligation to more carefully evaluate whether there is a full degree of added uncertainty.

Response: The NAS explicitly states: *"It is vital to select uncertainty factors that reflect the quality and relevance of the data, differences between test species and humans, and variation within the human population. Typically, in the past the permissible human exposure has been reduced by a factor of 10 for each additional source of variation or uncertainty"* (NRC (1993), executive summary, p. 6). OEHHA agrees that only using a factor of 10 is too limiting and may ignore contributions made by chemical-specific data. For this reason, the technical support document uses uncertainty factors in the range from 1-10, depending on available data. For example, for benchmark calculations, the interspecies UF for animal studies and the intraspecies UF for human studies has been changed to 3. Similarly, for sensory irritation, the uncertainty factor for LOAEL to NOAEL extrapolation has been reduced to 3. Dourson and Stara (1983, p. 228) stated that, based on their data *"it seems somewhat reasonable to employ a 10-fold uncertainty factor to account for intraspecies variability in lieu of chemical-specific toxicity data."*

Comment: In the case of nickel, insoluble nickel appears unlikely to cause the acute hazard effects indicated. Sources wishing to distinguish between soluble and insoluble nickel compounds emitted should be able to reduce calculated hazards accordingly.

In the Determination of Acute Toxicity Exposure Levels for Airborne Toxicants, OEHHA indicates that the acute hazard impact for nickel is based upon testing in 1978 by Graham *et al*. This study did report a potential immunotoxicity suppression effect in mice at inhalation doses of 250 $\mu g/m^3$ nickel, and no effect at inhalation doses of 110 μg/m3. However, there was some uncertainty as to the significance of the effect. At most the effect appears to be an 11% decrease in cell production attributed to a four times higher nickel chloride dose. Also, the report in question includes data for three nickel compounds: nickel chloride, nickel sulfate and nickel oxides. For the sulfate and oxide, the effects were about the same at 12 mg Ni/g body wt as at 3 mg Ni/g body wt, and about equal to the zero exposure data point for $NiCl_2$. Only $NiCl_2$ showed any consistent effect at increasing dose. Furthermore, a greater effect (lower plaque production) was observed in one of three exposures to dilute hydrochloric acid (HCl at pH=6). That leaves it uncertain whether it is the nickel ion, the chloride ion, the specific compound, or some testing artifact which contributed to this limited effect observed. The actual data was:

Log10 plaques per 10^6 cells			
Dose (µg/g Ni)	**$NiCl_2$**	**$NiSO_4$**	**NiO**
0.00	**2.63**	**2.86**	**2.71**
3.09	**2.57**	**2.67***	**2.60**
6.17	**2.47**	**2.53***	**2.38**
9.25	**2.37**	**2.64***	**2.59**
12.34	**2.29**	**2.63***	**2.66**

HCl Test Data (Log_{10} plaques per 10^6 cells)	
Test Number	**Test pH=6**
1	**2.7**
2	**2.58**
3	**1.9**
4	**2.62**

Response: The data shown in the comment are <u>not</u> the data upon which the REL for nickel was based. The comment shows the dose-dependent suppression of antibody-forming cells (or "plaque-forming cells") by intramuscular injection of nickel salts and nickel oxide. These data substantiate the systemic immunotoxic effect observed following inhalation exposure to the same compounds. In addition, the degree of suppression of the antibody response stated in the comment, 11%, is inaccurate. The actual suppression in antibody cell production in the data shown above is up to 55% compared to controls because the suppression data are on a logarithmic scale. In addition, the true degree of suppression in the data upon which the REL is based is closer to 25% at the LOAEL based on historical data, although the number of plaque-forming cells in the controls is not shown (see Fig. 3 of the Graham *et al*. (1978) reference).

The use of the hydrochloric acid pH=6 data is inappropriate since these data were collected following intramuscular injections in a different experiment. These data are also shown out of context in the comment. The original paper shows that the four pH groups (not shown in the comment) showed no significant differences from concurrent controls. The authors therefore concluded, on page 80 of the paper, that despite the single datapoint of 1.9 (which apparently

contained one spurious replicate), there was no significant influence of pH on the intramuscular injections of the metals studied.

Comment: If this study were to be the primary basis for addressing nickel hazards at the 100 to 250 $\mu g/m^3$ range, as OEHHA suggests, then there ought to be considerable doubt whether the nickel sulfate or oxides more typically emitted by power plants pose the same risk as the nickel chloride.

Response: It is true that nickel oxide was not shown by Graham *et al*. (1978) to have an immunosuppressive effect when given intramuscularly. Nickel oxide was not tested by inhalation by Graham and colleagues. Since no inhalation immunotoxicity data for nickel oxide or other insoluble nickel compounds were collected, there is insufficient evidence to categorize nickel oxide separately from other nickel compounds. Nickel sulfate showed distinct suppression of the antibody response at all levels tested when animals were exposed to nickel intramuscularly. In addition, mice exposed to nickel chloride or nickel sulfate by inhalation were significantly more susceptible to streptococcal infection than controls (Adkins *et al*., 1979). This finding further strengthens the hypothesis that inhaled nickel produces biologically significant suppression of pulmonary defenses. Nickel oxide was not tested in the Adkins *et al*. report.

Comment: Furthermore, by definition, insoluble nickel is less likely to be rapidly absorbed by the body, and any acute hazard exposure effect is more likely to be dependent upon soluble nickel exposures than upon insoluble nickel exposures. If insoluble nickel causes adverse effects, that is more likely to be a chronic effect, where the longer term presence of insoluble nickel compounds in the body might be a compensating factor for the poorer body chemistry access to those compounds. We therefore suggest that OEHHA limit its acute nickel hazard REL to soluble nickel. Such a factor would apply to total nickel where sources did not distinguish in their emission inventories between soluble and insoluble nickel emitted. But sources should be able to collect such data, and reduce calculated acute hazards accordingly.

Response: OEHHA agrees that the theories presented in the comment are plausible. However, since there are no actual data to evaluate immunotoxicity separately for each nickel compound, OEHHA cannot develop separate RELs for speciated nickel compounds at the present time.

Comment: Historically, workers have been exposed to peak and chronic soluble and total nickel exposures far in excess of the proposed REL. For example, the Report of the International Committee on Nickel Carcinogenesis in Man, February 1990, reported on page 24 that the medium nickel concentration from 3044 air samples was 130 $\mu g/m^3$ in Oak Ridge location, and that about 70% of the Oak Ridge workforce were in two other locations where nickel concentrations exceeded 1,400 to 1,800 $\mu g/m^3$ in at least 10% of the measurements. On page 25, it was noted that there were areas where average nickel concentrations exceeded 10,000 $\mu g/m^3$ over working lifetimes. With all of those historically high human exposures, OEHHA has made no recommendation for exposures causing lethal or serious effects, and only cites complaints of

irritation and headaches after four weeks of exposure in the 70 to 1100 $\mu g/m^3$ range, (mean = 440 $\mu g/m^3$), and skin sensitivity at a level not stated.

Response: OEHHA thanks the commentator for the review of workplace exposure levels for nickel compounds at Oak Ridge. The data mentioned by the commentator describe health effects that are more severe than those addressed by the RELs and may be useful for the determination of the severe adverse and life-threatening effects.

Comment: As indicated on the attached spreadsheet, it is possible for relatively small and common oil combustion sources to have total calculated acute hazard indices approaching 20% to 50% of the 1.6 $\mu g/m^3$ level. At that level, ARB guidelines suggest T-BACT should be required (particulate control for all new diesel engines?). Furthermore, several such distillate oil sources located together, or just one residual oil source with a small stack and close neighbors, could easily cause the calculated acute hazard index to approach or exceed one, at which point most risk managers require notification of impacted neighbors, denial of new or modified source permits, and shutdown of existing sources unable to come into compliance within five to ten years. All this for impacts that remain far below any lowest observed effect level. A review of the assumed factor of safety for nickel may be more appropriate than the control, prohibition or shutdown of all oil combustion sources. If OEHHA does not wish to undertake such review, we suggest that OEHHA at least provide for the possibility that the appropriate risk management agencies might prefer to gather information on what effect an alternative factor of safety assumption for nickel might have on the calculated acute hazard index, before deciding whether to actually require such notification, control, prohibition, or shutdown based solely upon the OEHHA factor of safety recommendation.

Response: The RELs in this document are health-based values derived from the most sensitive endpoints reported in the scientific literature. Considerations of mitigation measures requiring expenditures by industries are risk management decisions, in which OEHHA is not involved.

After reviewing the literature, OEHHA has calculated an acute REL for nickel of 3.3 $\mu g/m^3$ based on the acute inhalation study conducted by Cirla *et al*. (1985) in asthmatics. Although the animal immunotoxicity data are highly suggestive of acute human health consequences for nickel exposures, the data collected by Cirla *et al*. contain considerably less uncertainty and are based on effects in sensitive individuals.

Comment: Factors of safety of 1000 relative to reversible effects of no great significance, such as mild eye irritation for acrolein, are unjustified.

Response: OEHHA considers eye irritation to be an adverse effect. Eye irritation is a mild adverse effect, unless it is of a severe or irreversible nature, in which case it is considered a severe adverse effect. Since a NOAEL was not identified in the human subjects in the key reference, an uncertainty factor of 10 was originally applied to the LOAEL for estimation of a NOAEL. As described elsewhere in the responses, an uncertainty factor of 3 is now being applied when

adjusting a LOAEL to a NOAEL for mild irritation. In addition, since individual variation exists in the human population, an uncertainty factor of 10 was applied. Therefore, the total uncertainty factor applied to the acrolein REL is 30. The duration of the study was only for 5 minutes, therefore a 1-hour value was estimated using a time-adjustment. The REL therefore changed from 1.2×10^{-1} to 3.6×10^{-1} µg/m³.

References:

Adkins B, Richards JH, Gardner DE. Enhancement of experimental respiratory infection following nickel inhalation. Environ Res 1979;20:33-42.

Dourson M, Stara JF. Regulatory history and experimental support of uncertainty (safety) factors. Regul Toxicol Pharmacol 1983; 3:224-238.

Graham JA, Miller FJ, Daniels MJ, Payne EA, Gardner DE. Influence of cadmium, nickel, chromium on primary immunity in mice. Environ Res 1978;16:77-87.

National Research Council (NRC). Committee on Toxicology. Guidelines for developing community emergency exposure levels for hazardous substances. Washington (DC): National Academy Press; 1993.

R2C2 Company

Comment: The guidelines do not seem to allow an assessor to offer an alternative to any of the RELs that have been promulgated by OEHHA. The spirit of SB-1732 would seem to be served better by allowing an interested party to offer an alternative assessment based on newer information than used in OEHHA's development of the REL or using newer methods to interpret old information. While OEHHA has expressed its intention to update the RELs as such new information or methods become available, its incentive to do so in a timely fashion is less than that for an interested party.

Response: OEHHA welcomes submission of new pertinent data or methodologies affecting the generation of RELs. Confusion and an uneven playing field would result if each assessor were to submit risk assessments based on different RELs. In addition, OEHHA's RELs undergo public and peer review. For these reasons, issues regarding the derivation of the RELs should be resolved through the public comment process and through review by the ARB's Scientific Review Panel.

Comment: The basic approach for establishing RELs is to apply uncertainty and modifying factors either to benchmark doses or to NOAELs/LOAELs. Both depend on defining what constitutes an "adverse" effect. The language in the Technical Support Document appears to be inconsistent in this regard. For example, Figure 2 on page 11 describes Level 1 as: *The level at or below which no adverse effects are expected. Exposure at or below this level may be perceived by mild irritation of the eyes, nose, or throat, or by unpleasant odors, tastes or sight. Other changes of uncertain physiologic significance may also be observed.*

This language, and that in the corresponding listing on page 10, seems to imply that mild irritation, sensory clues, and physiologic changes without clear clinical significance would not be considered adverse for the purposes of defining a NOAEL. Yet in Table 1 (on page 9) mild irritation, unpleasant sensations, and findings of statistical significance but uncertain clinical significance are all shown to occur above Level 1, which is described as "discomfort." In its development of the RELs, OEHHA has apparently used the more restrictive definition of adverse. Because of the mechanical interpretation of state guidelines by some local air districts, I fear that the occurrence of "unpleasant odors" on one day per year at a location that may not be inhabited by anyone at that time may be interpreted as equivalent to a chronic exposure to annual averaged concentrations that might cause a serious neurologic condition or cancer. In other words, using such a restrictive definition of "adverse" for acute toxicity may trivialize the whole risk assessment endeavor.

Response: Unfortunately, the draft incorrectly described the Level 1. The definitions for the severity effect levels have been corrected in the revised draft. We have tried to define the acute, adverse, non-cancer health effects such that local Air Districts and other risk managers can calculate hazard indices and prioritize risks accordingly. The toxicological endpoint is clearly stated for each acute REL, and for each hazard quotient calculated in any risk assessment.

Comment: The procedure for adjusting observed dose-response relationships to one hour when data were obtained for a different exposure duration uses default procedures that are "conservative" for durations either longer or shorter than one hour. While this procedure may be appropriate for substances with only one duration represented by the available data, it could be excessively conservative if data for durations bracketing one hour are available, because the procedure for durations longer than one hour could underestimate the NOAELs for durations under one hour and vice versa. It is not clear whether OEHHA would always derive an empirical value for n in these situations.

Response: If multiple dose/duration data are available for the same endpoint and species, we have derived the exponential term for the modified Haber's relationship (for example, see the ammonia summary). OEHHA welcomes the submission of analyses of new data sets that may help pinpoint this exponent for specific chemicals.

Comment: The discussion of exposure assessment and risk characterization in the guidelines states that 1-hour maximum concentrations for each substance should be calculated for each substance and the hazard quotients and hazard indexes derived accordingly. There is a danger that a user could derive a hazard index based on maximum hazard quotients that occur at different places or at different times of year because of different locations or characteristics of the sources for different substances. While methods exist for overcoming this difficulty, OEHHA should be sure that the exposure assessment guidelines adequately cover this issue and that appropriate cross-references are made in the acute toxicity guidelines.

Response: This issue will be addressed in the upcoming Risk Assessment Guidelines.

Comment: Both Table 1 of the draft guidelines and Appendix B of the Technical Support Document show the toxicologic endpoint for hydrogen sulfide to be "respiratory irritation." The discussion of hydrogen sulfide in Appendix C of the Technical Support Document makes it clear, however, that the REL (which is also the California ambient air standard) is set at the odor detection level. Statements at the workshop confirmed that the REL for H_2S is based on odor. The listing in the Tables is probably an artifact of the old CAPCOA guidelines, which erroneously implied that H_2S is a respiratory irritant at levels only slightly above the REL. The listing should be changed because users may erroneously calculate the hazard index for respiratory irritation to include the hazard quotient for hydrogen sulfide.

Response: The comment raises a valid and difficult issue. The 1-hour CAAQS values were uniformly adopted by OEHHA for use as 1-hour Level I RELs. This was the case for H_2S. The comment is correct that the CAAQS is based on odor perception. An REL based on bronchial obstruction in asthmatics exposed to 2 ppm H_2S for 30 minutes (Jappinen *et al*., 1990) would be 0.1 ppm. However, because the CAAQS is not based strictly on respiratory irritation or other adverse effects that can be summed in a hazard quotient, OEHHA is changing the REL for H_2S based on the bronchial reactivity observed in the Jappinen *et al*. (1990) study. The new 1-hour

REL is 0.1 ppm (140 µg/m^3). Thus the REL has changed from 42 µg/m^3 to 140 µg/m^3.

Santa Clara Manufacturing Group
(Comments submitted by IBM, Center for Product and Process Toxicology)

The Group's main comments were the following

With respect to ethylene glycol monobutyl ether (EGBE) Level I:

Comment: Safety factors of 100 to 1000 are inappropriate for toxicological endpoints such as irritation. The ACGIH usually sets the level just below the known irritation level for humans. A factor of 2 or 3 is more conservative and appropriate.

Response: The REL for EGBE has been recalculated and is now based on reproductive and developmental effects, a serious adverse effect. The REL has thus been changed from 5.5×10^3 to 1.2×10^4 µg/m³.

Comment: Regarding the Level II: In light of the minimal developmental effects observed only in the presence of significant maternal toxicity, it might be appropriate to either declare that EGBE is not a developmental toxin or significantly adjust the safety factor that is used to determine the REL...In further support of the inadequacy of the REL for this compound, it should be noted that the dams in the developmental study showed significant damage to the erythrocytes. It is entirely possible that some portion of the maternal toxicity (and thus stress on the developing fetuses) was related to the lysis of erythrocytes in the exposed dams.

Response: The severe adverse effect level for EGBE has been reevaluated to reflect previous comments. This level is now the REL and is based on reproductive and developmental toxicity data in rabbits, rather than rats, to more accurately reflect the human susceptibility to EGBE.

Comment: As a final point, the table on page 18 of Part 1 of the Draft Document indicates that the toxicity concerns for the regulatory level were both sensory irritation and reproductive and developmental toxicity. In reality, the lower number is always selected; for EGBE this would be the number for Level I.

Response: In the case of EGBE, both irritation and developmental and reproductive toxicity were listed as endpoints of concern because of the close proximity of the threshold for the two endpoints. The table in question has been changed to reflect the new REL.

Society of the Plastics Industry

General Comments

Comment: SPI strongly urges OEHHA to cease further development of reference exposure levels (RELs) for chemicals under the Air Toxics Hot Spots Program until the Proposed Guideline is finalized. Currently, OEHHA lacks an adequate screening mechanism for prioritizing chemicals for review. The Proposed Guideline should be revised to include screening criteria, and the extent of atmospheric releases should be the key to the screening exercise. A chemical substance may be highly reactive or disperse readily, even though there are significant toxicological concerns associated with it based on published data. It would not be a valuable use of the state's resources to list as high priority for review such chemicals whose actual emissions may be quite low.

SPI also believes that California can greatly simplify its proposed approach by adopting a more flexible framework for risk assessment. With all of the advances in risk assessment, it can only benefit the State of California to be as forward thinking as possible instead of setting in regulatory stone certain prescribed methodologies that may become outmoded, or which may not be appropriate in all cases. In short, any reasonable and scientifically supportable approach for assessing exposure should be acceptable, and OEHHA should not prescribe and limit the approaches, as now proposed. OEHHA should not foreclose the use of previously formulated acute exposure values, which may, in certain cases, be reasonably modified consistent with OEHHA's mandate. In any event, the final guideline should require that OEHHA explain the basis for selecting the method used in conducting individual risk assessments on specific chemicals, and provide information on why the method selected is the preferred approach for the chemical(s) under review.

Emission-based screening criteria and a more flexible approach to risk assessment are consistent with the state's mandate, and with the widely accepted procedures used by the National Academy of Sciences (NAS) (cited in the proposed Guidelines). We believe they have value to contribute to the state and the regulated community.

Response: OEHHA agrees that emission-based prioritization for screening of chemicals is a vital part of the hazard prioritization process. OEHHA also recognizes the needs of the local Air Districts to identify chemicals of concern being released in their area. It is for these reasons that chemicals with high emissions such as toluene, methanol, benzene, styrene, phenol, and chloroform were added to the list of 32 chemicals already identified by the California Air Pollution Control Officers Association in 1993 for the development of acute non-cancer RELs. In response to the commentator's concerns, the Technical Support Document has been modified to acknowledge that emission rate was a major factor in prioritizing chemicals for REL development.

Comment: OEHHA discourages the use of previously formulated acute exposure values to determine the REL.

Response: OEHHA has evaluated existing acute exposure values. If appropriate acute exposure values existed, they were adopted (e.g. 1-hour CAAQS values). Most of the existing values were created for entirely different purposes, such as workplace conditions (ACGIH-TLVs), emergency planning for military personnel (NAS-EEGLs), or accidental release scenarios (AIHA-ERPGs), or the values did not address the protection of sensitive individuals (e.g., many of the AIHA-ERPGs).

Specific Comments and Concerns:

Comment: The 54 chemicals in the Guideline TSD appear to have been chosen arbitrarily. The Guideline should reflect the extent of atmospheric emissions.

Response: The chemicals in the Technical Support Document were chosen in a methodical manner. As described in Table 2 of the Technical Support Document, the 32 chemicals previously identified by the California Air Pollution Control Officers Association (CAPCOA) in 1993 as chemicals for acute reference exposure level development were included; one additional criteria air pollutant not in the CAPCOA document was included. Sixteen (16) additional chemicals with high emissions were addressed, as were 4 other known toxic compounds.

Comment: OEHHA should cease reviewing substances until criteria for review based on exposure are developed.

Response: Criteria for review are cited above and include emission volume.

Comment: OEHHA should provide a weighing system that includes an assessment of whether the conditions of the study reflect a realistic air emissions scenario. OEHHA should emphasize that not all studies are equal and should not be treated equally in risk assessment.

Response: We have used the best available toxicological data in generating the acute exposure levels in this document. Only inhalation data were used. Where deficiencies in the data exist, we have endeavored to point out these flaws in the derivation section of each REL in the TSD. In the interest of brevity, we have limited the discussions on these issues to the most critical points.

Comment: OEHHA should adopt a more flexible approach to setting REL values and avoid prescribing methods to apply in every case. OEHHA uses various methodologies to determine the RELs in an arbitrary manner. It should be stated why a particular method was chosen for each case.

Response: The Technical Support Document uses the best current data for determining the RELs. The methodology for development of the RELs follows a defined procedure. If a benchmark dose calculation could be made with the data, the benchmark concentration was OEHHA's preferred method of deriving an REL. If the data were not appropriate for calculating a benchmark dose, a

NOAEL or LOAEL was used with appropriate, clearly defined uncertainty factors. To our knowledge, benchmark dose methodology has not been used in any other regulatory setting. A modified Haber's relationship was used to obtain greater accuracy in describing the effects of duration as well as concentration of exposure.

Comment: OEHHA should adopt the approach in U.S. EPA's Final Guideline for Estimating Exposures.

Response: The EPA Guidelines referred to in this comment do not pertain to the setting of health effect levels, but rather to exposure assessment and modeling, which are described in another document by OEHHA: *Technical Support Document for Exposure Assessment and Stochastic Analysis*.

Comment: OEHHA should review and recognize other existing acute exposure levels, including those produced by California OSHA and ACGIH.

Response: OEHHA has reviewed the occupational standards mentioned and others in the Technical Support Document. In most cases, these values were not appropriate for the determination of health-based reference exposure levels for the general public.

Comment: The use of a modified version of Haber's Law is not well substantiated for use in assessing exposure and should only be used if a range of acceptable values for the exponential term, n, is used in the calculation.

Response: Methods for REL development should not be confused with methods for assessing exposure. The use of modified Haber's relationship is an attempt to bring more accuracy to estimating the effects of a 1-hour exposure from the experimental literature. Where the data allow the derivation of the exponential term in the modified Haber's relationship, OEHHA has used the data to its utmost ability. For all of the chemicals with sufficient information from which to derive an exponential term, this method has been successful. For example, the chlorine, phosgene, and ammonia data sets illustrate the relationship between concentration and duration as described by the modified Haber's relationship. Since most chemicals lack sufficient time-concentration data for the adverse effects of concern, OEHHA has proposed a value for "n" that is approximately midway in the range of empirically determined outcomes. The alternative presented by the comment would be confusing. Using all values determined empirically would require the impractical expectation that a risk manager decide which value of "n" to use.

Comment: The benchmark dose methodology currently has no precedent for use in risk assessment and is not standardized. Until it is standardized, OEHHA should report the range of the entire 95% confidence interval to define the critical exposure in developing a REL. The use of

the entire range of values avoids the impression of certainty that accompanies the use of a single value.

Response: It is true that there is no precedent for using a benchmark concentration approach in risk assessment, therefore there are no existing standards. For this reason, OEHHA has proposed the benchmark concentration approach in the Technical Support Document as a step towards achieving a standard. While it is always true that different data sets will necessarily be of varying quality, the benchmark concentration does more to account for experimental variability and sample size by considering the confidence bound on the dose-response slope than any other existing method. By selecting the lower end of the confidence limit, OEHHA is following prudent public health protocol, and choosing to lean to the side of safety. Published discussions on benchmark dose methodology support this position (Alexeeff *et al*., 1993; Auton, 1994; Crump, 1984). Because OEHHA uses the lower bound estimate on dose for the derivation of the REL from a benchmark calculation, we also have lowered the uncertainty factor applied to the REL for either interspecies extrapolation (animal studies) or for sensitive individuals (human studies) from 10 to 3. This illustrates "flexibility" in treating uncertainty when appropriate data exist. If the upper bound were to be used, as suggested in the comment, there would be no justification for the lowering of the uncertainty factor, and in fact would justify use of a much larger uncertainty factor.

Comment: OEHHA should clearly articulate the nature and magnitudes of uncertainty associated with risk estimation to be in accordance with the NRC Committee on Risk Assessment (1994).

Response: In the Technical Support Document, OEHHA has endeavored to explain the rationale for all options used to account for uncertainty. Certain assumptions were required in order for the risk assessment process to be consistent, accurate, simplified and health protective. The NAS guidelines acknowledge the need for default options, and support the use of these options when data-specific factors are not available.

Southern California Edison Company

Comment: We are concerned that for some substances, nickel for example, the REL has been determined solely by laboratory findings on animals of unknown clinical significance or pathologic consequences in humans. In the case of nickel, an artificial challenge (injection of sheep blood cell product) and an artificial measure of immune response (numbers of antibody producing cells harvested from the spleen) were used on laboratory animals as an experimental surrogate for evaluation of health impact to humans of environmental exposure to air pollutants. A 100-fold margin of safety is then used to create the REL to protect health.

This approach follows from the statements in the document that the most sensitive endpoint of toxicity should be used for the risk assessment process. However, the relevance of the most sensitive endpoint found in the literature, in the case of nickel being subtle biochemical changes of unknown clinical or physiologic significance, is not at all clear. Such laboratory experiments are useful in assessing the potential for effects, and in determining what endpoints to look for in humans. However, without clinical or other data of relevance to humans, their use in setting standards of exposure is dubious at best. There were no discussions on whether nickel exposure might be expected to produce effects on an infectious process in humans, for example.

Response: The general concern raised in the comment is about the use of laboratory tests of unknown clinical significance as the bases of the RELs. Immunotoxicity tests such as those performed in the laboratory animals are highly invasive procedures and are not possible in humans, therefore it would be virtually impossible to duplicate these findings in human subjects. However, the vital importance of the immune system to human health is clear and should not be dismissed as irrelevant. The laboratory test in this case (antibody response to sheep erythrocytes), although "artificial" by definition, is a standard toxicological method that has one of the most useful immunotoxicological endpoints (Luster *et al*., 1992). The mouse model and test procedure described measure immunological events that are analogous to events that occur in the human antibody response.

To further illustrate the immunotoxicity of soluble nickel aerosols in mice, Adkins *et al*. (1979) showed that a 2-hour exposure to 450 $\mu g/m^3$ nickel in the form of nickel sulfate and 500 $\mu g/m^3$ nickel in the form of nickel chloride resulted in significantly increased mortality (21-26% above controls) in mice challenged with a streptococcal infection. No adverse pulmonary effects were observed in these mice. This finding illustrates the importance of the suppressed immune function endpoint at a slightly lower concentration (250 $\mu g/m^3$) described in the Graham *et al*. (1978) study, even though the mechanism for immunotoxicity has not yet been established. A detailed summary of the Adkins *et al*. (1979) reference will be added to the Technical Support Document.

The nickel REL has been changed from 1.6 to 3.3 $\mu g/m^3$ and is now based on adverse pulmonary effects following a specific nickel challenge in human asthmatics.

Comment: Also, there were no recommendations for effects levels for Tier II or Tier III effects. Are we to presume that there are no serious adverse effects to humans from short term exposures to nickel? And if none are listed, why is there a need for such a low level for a REL?

Response: The reason that there are no more severe toxicity levels for nickel in the Technical Support Document is that there simply are no available data, human or animal, useful for generating such levels. When more data become available, severe and life threatening levels will be derived.

Comment: To protect against effects that are described as mild, and which include things such as irritation, bronchoconstriction, headache and the like, makes sense from a public health point of view, as these are often connected to more serious effects at higher exposure levels. But to use "mild effects" such as changes in biochemical activity or cellular manifestations that are not known to be relevant to a clinical process, makes no sense from a public health point of view. The usefulness of such data is to assess the mechanism of any clinical effects, and to assess the level of any margin of safety that might be appropriate for setting a health based standard. Not to set the standard. To use only such "effects" to set a health protective standard may result in expenditure of significant funds to abate exposures, with little if any health benefit. This is not sound public health policy.

Response: Sensitive physiological endpoints measured in toxicology studies may not always be detectable in routine clinical settings (i.e., in humans). For example, low-level exposures to carbon tetrachloride may result in significant liver changes that are not easily detected in a clinical setting, yet these changes define the starting point of a known toxicological process. It would not be prudent public policy to allow known toxicological effects to be ignored simply because routine clinical tests to detect this effect are not available. OEHHA has carefully considered the use of relevant biochemical tests for the development of RELs. When such test results were inconsistent with known clinical effects, they were not used as the basis for RELs.

Comment: For substances where there are only these laboratory findings of unknown significance, we propose for Tier I RELS an alternate approach. That is, that a lower margin of safety than 100 be used. The rationale is two-fold. First, such Tier I RELS are defined as biochemical or physiological changes of uncertain clinical significance. Since by definition no pathologic health effects can be demonstrated at this level, we suggest a health protective safety margin of 10, or even 1 applied to a NOAEL is sufficient. Second, the RELS are to be used to determine potential health risk of living or working near facilities. Facilities with potential health risks above certain levels must notify neighbors of the potential risk and reduce that risk. Considerable expense is involved in producing and notifying the public about the results and in reducing exposures. Equally important is that the information produced be relevant to the real potential for adverse health risk.

Response: OEHHA does not use effects of unknown clinical significance for REL derivation. However, effects that are subclinical are used, if these are consistent with more severe effects

observed at higher concentrations. Uncertainty factors for interspecies differences and individual variation are applied to the RELs in a consistent manner. The clinical significance of immunotoxicants is unknown but plausible. OEHHA considers mild, transient changes in immune function tests to be a mild adverse effect. Certainly, a decrease in a child's or an adult's ability to fight infection is an adverse effect. It is clear that immunologically compromised individuals (e.g., people with various types of immune deficiencies or autoimmunities) exist. There is therefore no justification to remove the uncertainty factor used to account for sensitive individuals. It is not known if humans are more or less susceptible than mice to the immunotoxic effects of nickel. In the absence of human immunotoxicity data, the uncertainty factor for interspecies differences is necessary.

Comment: It is a disservice to the public to warn of possible health risks based on methodologies so conservative as to bear little possibility of existence. While we recognize many uncertainties exist, we believe the best science should be used to establish RELS which are relevant to human exposure to pollutants which do not incorporate overly conservative elements.

Response: It is not OEHHA's intent to be over-conservative in setting these values. OEHHA uses methodology that is consistent with the NAS and USEPA. The intent of RELs is to protect against any adverse health effect. In this regard, the RELs are not overly conservative.

Comment: Finally, we have one additional concern about the RELs. Several metals are listed as the metal and its compounds (such as nickel, arsenic and selenium). These metals and their compounds have different chemical characteristics, such as solubility and potential biological/pharmacokinetic effects and behavior. A single REL for the metal and its compounds is unlikely to be appropriate. We believe separate RELs should be developed, as appropriate, to account for these differences in different compounds or groups of compounds with similar characteristics, to provide input for meaningful potential health risk information.

Response: Where data are available to identify effects attributable only to a specific metal compound, those data should be considered. It is rare that such a situation exists. In addition, the emissions data evaluated in the risk assessments are not speciated, but rather are reported as the proportion of the compound that is the metal. In practice, then, it is difficult to apply a specific compound REL to the data used in risk assessment unless and until those data are reported as a specific metal compound.

References:

Luster MI, Munson AE, Thomas PT, Holsapple MP, Fenters JD, White KL, *et al*. Methods evaluation: Development of a testing battery to assess chemical-induced immunotoxicity: National Toxicology Program's Guideline for Immunotoxicity Evaluation in Mice. Fundam Appl Toxicol 1988;10:2-19.

Luster MI, Portier C, Pait DG, White KL, Gennings C, Munson AE, Rosenthal GJ. Risk assessment in immunotoxicology I. Sensitivity and predictability of immune tests. Fundam. Appl. Toxicol. 1992;18:200-210.

Texaco Incorporated

Comment: It is inappropriate to add background concentrations of criteria air pollutants in AB 2588 risk assessments to a given facility because 1) background concentrations include non-stationary sources which are beyond the scope of AB 2588, and 2) background concentrations already include the contribution from individual facilities and to include background concentrations to the facility risk assessment essentially double counts the facility emissions.

Response: OEHHA has removed this suggestion from the document.

Comment: The purpose of AB 2588 is to address human health risk issues. It is inappropriate to develop acute RELs based on aesthetic criteria such as odor or taste (e.g., H_2S, copper). The H_2S REL should be developed based solely on sensory or respiratory irritation. The development of a copper REL should be delayed until better quality and relevant data becomes available (see 10. Copper REL).

Response: The definition of the effect severity levels has been corrected and only adverse effects, not organoleptic effects such as odor or taste, are considered for REL development. The RELs for copper and H_2S have been revised and are no longer based on odor or taste.

Comment: The draft guidelines document states that, "When two chemicals that impact the same toxic endpoints given together the most common observation is that their effects are additive ...the interaction of two or more chemicals is assumed to be additive." (P. 10, 3rd paragraph). Although chemicals may affect the same target organs, they may work through different mechanisms of action and the combined effects may not be additive. Thus, only the hazard quotient (HQ) of chemicals affecting the same target organs and with the same mechanism of action could be summed. Even under these circumstances the activities could be competitive and the effects not additive.

Response: Assessing the toxicity of complex mixtures is difficult. According to the comment, only chemical toxicities with the same mechanisms should be summed in a hazard quotient. However, most chemicals have multiple mechanisms of toxicity. Additionally, multiple indirect influences on organ physiology cannot be disregarded simply because the molecular or cellular targets of two chemicals are not identical. For example, one chemical may influence the toxicity of another chemical by inducing metabolic enzymes or by decreasing intracellular glutathione, even though the "mechanism" of toxicity of the two chemicals may be quite different. In fact, when considering the full complexity of this issue, it must also be acknowledged that potentiation and synergism (supra-additivity) likely often occur and are not accounted for. Adding a mechanism of action parameter to the risk assessment methodology would create an additional layer of complexity and would require many chemicals to be placed in an "unknown mechanism" category. OEHHA believes that the best approach is to add hazard quotients by target endpoint.

Comment: For those substances currently without toxicity criteria and not undergoing dose-response analysis by OEHHA due to insufficient data in the open literature, adequate yet unpublished toxicity data within industry may be used to develop RELs. As more than one such data set may be available, the selection of the most appropriate data set to develop RELs should go through the public review process before the RELs are adopted.

Response: It is true that there may be appropriate data for REL development that are not examined and used. These studies are not always directly available to OEHHA. One important function of the public comment process is to alert OEHHA to pertinent studies that may not have been considered in developing RELs. Several of OEHHA's proposed RELs are based on unpublished data from industry and academic settings. Regardless of the origin of the data, all of the RELs are undergoing public comment, and will be reviewed by the Scientific Review Panel.

Comment: An HI of greater than 0.5 is proposed for use as a cut-off for requirements on 1) presenting an acute HI isopleth map, and 2) providing information on the emitted chemicals which can impact the endpoint and have not been included in the HI calculation. This cut-off is inappropriate since by the definition of an HI, only an HI of greater than 1 would indicate a concern for a potential hazard. An HI of 1 is the more appropriate cut-off.

Response: OEHHA has withdrawn this proposal.

Comment: The RELs for all metals are presented as, "for X metal and compounds". As the study used for the development of an REL is based on the most toxic metal form, it is overly conservative to use such REL for less toxic forms. The less toxic forms of metals should be considered separately, e.g., separate RELs based on specific chemical compounds should be developed.

Response: If data exist for speciation of grouped compounds, OEHHA agrees that specific compounds may be considered separately. However, for the metals in the Technical Support Document, data exist for predominantly one form and this is usually the most toxic form. In addition, emissions data are usually not speciated and the form of the metal emitted is unknown. If reliable data do not exist for a given species within a group of compounds, then OEHHA's approach is that the default for that compound should be one which is more likely to lean toward public health protection.

Comment: In order to enhance the consistency in selection of appropriate toxicity data for the development of RELs, documentation of selection criteria is needed. More specifically, the following criteria need to be clearly documented: 1) data quality, e.g., studies with one dose should not be used, 2) relevancy to humans; 3) significant toxic endpoints, e.g., immunotoxic endpoints (see discussion below).

Response: The criteria for the above mentioned points are as follows. Data quality: all data are considered, even those that are not published or formally peer reviewed. Since there are exceptions to almost every rule or criteria, some expert judgment must be used. For example, free-standing NOAELs (FSN) are undesirable for several obvious reasons, including lack of dose-response, potential that the study was not measuring the critical effects, etc. However, there are cases in which a FSN is felt to be the best data for study-specific reasons. These reasons and decisions are different for each case. It is therefore not practical to list a defined set of criteria that contain so many potentially unforeseen caveats. The rationale for the selection of the key reference for each REL is presented for each chemical. Important issues regarding the quality of the data and significance of the endpoint are also discussed under the individual compound. Public and peer review assist us in identifying alternate available data. We revised several of the values based on data submitted in the comments.

Comment: Currently, the functional significance of immunotoxicologic responses has not been clearly defined. The immune system has functional reserve capabilities. The magnitude and type of immunotoxic responses which will result in functional disruption at levels which warrant regulatory actions have not been defined. Further, many immunotoxicity testing methods remain to be validated, and the relevance of animal data to humans is yet to be determined. Using animal immunotoxicity testing results to make inference to human health impact is, therefore, rather premature. Thus, the RELs for benzene and nickel and nickel compounds should be redeveloped considering other more appropriate health endpoints.

Response: It is true that the immune system has some functional reserve capacity. The same can be said for the liver, kidney, most epithelial tissue, and a host of other tissues/organs. To some extent, every cell has some reserve functional capacity. This does not mean that the immune system is refractory to toxicologic effects. The immune system has been well studied and is highly conserved between humans and other mammals. The mouse has been the standard laboratory model for immunotoxicity testing. Immunotoxicology has developed into a distinct, well studied discipline and has been accepted by the National Toxicology Program (Luster *et al*., 1988). Though immunotoxicity testing has not been performed on humans, many individuals have considerable variability in functional reserve capacity. To ignore the immune system as a potential target for toxicity would be inappropriate.

Comment: Documentation is needed for the procedures on updating RELs as well as the ACE 2588 program when new information becomes available.

Response: OEHHA welcomes new data or analyses of existing data that may contribute to improvement of the RELs. We will review and critique each set of data and add these to the REL document, if appropriate, in upcoming iterations of the acute Technical Support Document. We currently foresee approximately annual updates of RELs. Any updates also go through public and Scientific Review Panel review. OEHHA plans to work with ARB to update the ARB's Health Risk Assessment program with new RELs.

Comment: The copper REL should be deleted because 1) the endpoint chosen, taste, is not a health endpoint and is inappropriate for this purpose, 2) the data quality of the study selected is poor, as acknowledged in the technical support document (P. Copper - 4, 2nd paragraph), "Because of the poor quality of the existing data, reevaluation of the REL for copper is recommended when better methods or data are available." In addition, since the data quality is poor, copper should not be listed until it can be justified.

Response: The endpoint chosen for the REL was metal fume fever, not taste. The data quality of the selected studies on which the REL is based is adequate for evaluating acute toxicity. Data in humans are valuable because extrapolation from animals is not necessary. Recent data indicate inhibition of macrophage activity in guinea pigs. This study would result in a REL of 6 $\mu g/m^3$ if used. However, the clinical relevance of the particular effect in this study is not understood. Therefore, we are using the available human data.

References:

Armstrong CW, Moore LW, Hackler RL, Miller GB, Stroub RB. An outbreak of metal fume fever: diagnostic use of urinary copper and zinc determinations. J Occup Med 1983;25:886-888.

Stokinger HE. Copper, Cu. In: Clayton GD, Clayton FE, editors. Patty's industrial hygiene and toxicology: Vol. 2A. Toxicology. 3rd ed. New York (NY): John Wiley and Sons; 1981. p. 1620-1630.

Working Group on Community Right to Know

Comments:

1) Add more Levels 2 and 3 for chemicals, especially those that have high potential for accidental release.

2) Add more chemicals to the list, beginning with the federal EPCRA list, the Clean Air Act "List Rule" list, and the New Jersey DEP/TCPA list.

Response: The primary purpose of the current document is to provide guidance for routine, not accidental releases. OEHHA has updated the severe adverse and life-threatening effect levels in the Technical Support Document. The development of these levels is limited by the availability of scientific information. The chemicals in the current document consist of those recommended by the California Air Pollution Control Officers Association (CAPCOA), those that are released in high volume within the state, and a few others known to be toxic. OEHHA is evaluating chemicals that subject to the Air Toxics Hot Spots Act. OEHHA thanks the commentator for the concern for public health.

UNOCAL Corporation

The comment raises several questions about the draft REL for ammonia, summarized below:

Comment*:* OEHHA overlooked human exposure data cited as: Johnston, J. Lagters[sic], L. Dailey, R. 1979 Biological effects of short term high level exposure to gases: Ammonia: Draft Final Report. Contract No. DAMd 17-19-C-9086. U.S. Army Medical Research and Development Command, Fort Detrick, MD.

Response: When final reports are available, we use them instead of drafts such as the one cited above. The final report, authored by Legters, L. (1980), mentions no human study performed by the above authors. Apparently, the data cited from the draft report arise from IBT (1973) (a report also cited in the comment), and were included in the OEHHA REL calculation.

Comment: The authors of the above study concluded that concentration of 50 ppm or less did not cause irritation or discomfort.

Response: The comment is correct in that this study did not indicate irritation as a symptom in the subjects at 50 ppm. The acute REL is based on a benchmark concentration (BMC) analysis of the available ammonia data for humans. The BMC analysis takes into consideration the variability of the data, the sample size of the study, and the percent of the population responding to the effect. This also allows the analysis to incorporate the percent responding at lower doses even if the response at the specific dose was not statistically different from controls in the study. Consequently, the complete dose-response trend is used in the calculation.

Comment: OEHHA should have included the data from McClean *et al*. (1979) in the benchmark dose calculation.

Response: McClean *et al*. (1979) was among the pool of literature OEHHA staff evaluated before performing the benchmark concentration calculations for the ammonia REL. The study was not used for REL development because: (1) the nasal airway resistance pneumotachography may not measure indications of chemical irritation and (2) it would be inappropriate to apply the effects following extremely short exposures (5 to 30 seconds) to those of 1-hour responses.

Comment: OEHHA should have included the data developed by Procter *et al*. (1988) regarding a study on ammonia exposure response of 10 human subjects.

Response: In their book *Chemical Hazards of the Workplace*, Proctor *et al.* do not describe human exposure studies to ammonia which they themselves conduct. The authors summarized the IBT data which they obtained from the U.S. Dept of Health, Education, and Welfare publication 74-136, *Criteria for a recommended standard...occupational exposure to ammonia*,

NIOSH (1974). These are the same IBT data that were summarized in the comment, and the same data which were already incorporated into the OEHHA ammonia REL.

In summary, the data that the comment suggests be added to the REL calculation for ammonia were already included in the benchmark concentration analysis.

Comment: The Emergency Response Planning Guidelines (ERPGs) evaluation of ammonia may be more appropriate than the OEHHA REL.

Response: The comment states that the AIHA ERPG committee's assertion that "...At this level [25 ppm], there may be some odor, but there should be no significant irritation." was based on the studies by MacEwen *et al.* (1970) and Industrial Bio Test Laboratories, Inc. (1973). Actually, the ERPG credits MacEwen *et al.* and Ferguson *et al.* (1977), but the ERPG text suggests MacEwen *et al.* (1970) and Industrial Bio Test Laboratories, Inc (1973) as support for their assertion. The ERPG is for accidental chemical release scenarios and is concerned with evacuation or shelter-in-place decisions. The Hot Spots program is addressing predictable intermittent releases, and is concerned with impacts on the general population from occasional relatively high one-hour exposures that are from routine operations. Therefore, the ERPG-1 values are not applicable as Reference Exposure Levels designed to protect even sensitive individuals from mild adverse effects from one-hour exposures.

Both the MacEwen and the Industrial Bio Test Laboratories, Inc. (1973) study data were incorporated into the benchmark concentration calculation for the ammonia REL in the draft document. Industrial BioTest's conclusions were discussed above.

Comment: Occupational standards which are higher than the ammonia REL indicate that the REL is excessive.

Response: It is preferable not to apply occupational standards to the case of the general population, when guidelines exist which have been derived specifically for the general public. Workplace standards are set for healthy workers, and as such, do not include sensitive populations such as infants and children, pregnant women, elderly persons, and persons with chronic diseases, such as asthmatics. ACGIH specifically mentions the inappropriateness of TLVs for exposures to the general population.

Comment: Animal data should be used to verify the human data, including a claim by Clement Associates (1990) that an animal subchronic NOAEL at about 50 ppm had been established.

Response: In general, human data are preferred over animal data because: (1) the application of animal data to the human case normally introduces additional uncertainty, (2) animals are especially poor subjects to test nascent irritation as they may not elicit observable symptoms, and 3) the use of subchronic data in the development of an acute level is not preferable. This is

especially true for irritant gasses such as ammonia, to which subjects can become inured over time (Ferguson *et al.*, 1997).

Comment: Background levels of ammonia may exceed the REL value; and, as such render the REL inappropriate. Ammonia is present in exhaled air at concentrations 2-10 fold lower than the REL. The odor threshold for ammonia is 5 ppm.

Response: The REL for ammonia has been revised to 4.5 ppm and is now based on the BC_{05}. Ammonia is a naturally occurring compound, and a small background concentration can be expected. Further, ammonia is expired and excreted. This does not alter the fact that ammonia exposure will cause irritation to certain people at low concentrations. In regard to odor detection levels, estimates of odor thresholds for ammonia vary widely. Henderson and Haggard (1943) reported the lowest detectable odor as 50 ppm. Ferguson (1977) determined the olfactory threshold of ammonia, in the presence of mixed odors, as a range of 10-20 ppm. Ruth (1986), however, in a review of published odor thresholds, cited the range of reported ammonia odor thresholds as 0.04-57.1 ppm. This variation probably reflects the differences in experimental procedures used in obtaining odor thresholds and the variation in responses within the general population.

Comment: Applying modifying factors to the benchmark dose was not appropriate "Because there is [sic] data indicating that potentially sensitive subpopulations with bronchial asthma and chronic obstructive pulmonary disease are not likely to be more sensitive to exposure to low levels of ammonia than "normal" individuals...". For this assertion, several human studies are cited : McLean *et al.,* 1979; Holness *et al.,* 1989; Campbell, 1988.
Response: The data from McLean *et al*. (1979) show that in the atopic subjects tested, there was no significant difference in nasal airway resistance between individuals with or without a past history of asthma. However, the exposures in this study were for only 5-30 seconds. It is inappropriate to conclude from this study that asthmatics are not sensitive to respiratory irritation from ammonia inhaled for longer durations. Data from this study suggest that irritation may <u>not</u> be the most sensitive endpoint for ammonia exposure. Only 11 of 23 subjects complained of nasal irritation after exposure to 100 ppm for up to 30 seconds, whereas all subjects showed significant increases in nasal airway resistance.

Workers exposed to ammonia in the Holness *et al.* (1989) study were neither asthmatics nor atopics and did not necessarily constitute a sensitive subpopulation. Only about one fifth of the exposed workers (approximately 12 workers) reported symptoms that the comment suggests are consistent with chronic respiratory disease. The spirometry results shown in Table V of the Holness *et al.* (1989) paper show that there were no indications of restrictive pulmonary disease or chronic obstructive pulmonary disease in either the control or the ammonia-exposed groups. Furthermore, Holness *et al.* (1989) state,

> While there were no differences [in prevalence in reporting of symptoms], the exposed workers reported that exposure in the plant aggravated some of their reported symptoms.

> This was true for cough, wheeze, nasal complaints, eye irritation, and throat discomfort, and 21% of the workers reported skin problems which they often related to specific aggravating factors in the workplace, such as a specific work area where ammonia exposures were likely to be high or exposure to the soda ash dust itself.

Campbell (1988) is cited as reporting a patient with severe emphysema who benefited from the ventilatory stimulation of aromatic ammonia ampules. Although interesting, this case report along with the above cited studies do not negate the possibility that there is variable susceptibility to ammonia irritation within the human population. A modifying factor is necessary to account for this variability.

In a study performed by Shim and Williams (1986), the authors concluded that odors are an important cause of worsening of asthma, and that ammonia-containing household cleaning agents were among the major causes of exacerbation of asthma described by a panel of responding asthmatic patients.

Comment: Based on the Schoeb *et al*. (1982) rat data, ammonia is primarily absorbed in the upper respiratory tract at low concentrations, and little or no ammonia gas enters the lungs making it unlikely to affect sensitive subpopulations.

Response: The rat respiratory tract is markedly different from that in humans; thus rats are poor models for respiratory tract toxicity. The complexity and length of the nasal turbinates makes it more difficult for many chemicals to pass into the lower airways in rats. In addition, rats are obligate nose-breathers, further increasing the influence of the nasal turbinates in preventing chemicals from entering the lung.

Comment: Sensitive persons not accustomed to ammonia exposure would not experience fright, panic, or disabling effects at 100 ppm.

Response: The EEGL for ammonia developed by the National Academy of Sciences Committee on Toxicology (NAS, 1987) states that some might find that exposure to 100 ppm is annoying and, in some individuals, may induce “panic resulting in fright”.

Comment: A larger pool of literature should be used in the benchmark dose calculation, and an uncertainty factor smaller than 10 should be considered.

Response: First, as mentioned, we considered all information available in the open literature. Second, the uncertainty factor used was 3, not 10.

Comment: The Level II needs to be reevaluated because the concentration suggested for this level does not cause disability or serious health effects.

Response: The severe adverse effect level has been revised from 100 ppm to 130 ppm and is based on a NOAEL for intolerable irritation in humans.

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Western States Petroleum Association

LEGISLATIVE COMMENTS: The following comments address preliminary concerns with the draft guidelines, relative to the legislative intent of AB 2588 and SB 1731:

Comment: OEHHA should expedite development of the revised guidelines. SB 1731 took effect on January 1, 1993. It is still not clear when the revised guidelines will be available for industry application. In the interim, facilities remain subject to the overly conservative and scientifically outmoded CAPCOA Guidelines. Despite the urgent need for the guidelines, it is imperative that OEHHA acknowledge the legislative intent of SB 1731, apply the best available science and incorporate full public and peer review into the guideline development process.

Response: At the time the comment was made, OEHHA had been working on the Air Toxics Hot Spots Risk Assessment Guidelines for over 2 years. OEHHA acknowledges the legislative intent of SB 1731, to write risk assessment guidelines that allow for supplemental information and include a "likelihood of risks" approach, and continues to apply the best available science. There is extensive peer and public review of documents associated with the guidelines development and the ARB's Scientific Review Panel is also reviewing all documentation for the guidelines. OEHHA has been working simultaneously on the exposure assessment and stochastic analysis, chronic noncancer, and cancer potency portions of the document, all parts of the SB 1731-mandated risk assessment guidelines.

Comment: Each set of supplemental guidelines should be considered individually and collectively to assure compliance with the legislative intent of SB 1731 (e.g., reducing uncertainty and compounded conservatism and use of best available science).

OEHHA should assure that the opportunity is provided for public review of the final risk assessment process once all of the revised guidelines have been issued, and prior to approving any of the individual guidelines, or finalizing the integrated process for conducting health risk assessments under the revised AB 2588 program. In evaluating the cumulative impact of the guidelines, it will be essential for reviewers to consider the interaction between the various component guidelines (acute, chronic non-carcinogen, carcinogen, and exposure assessment). To achieve this review, OEHHA should incorporate an additional, extended public review period for the completed revised risk assessment process before any action is taken to finalize and/or approve any of the component guideline documents.

Response: Public and Scientific Review Panel (SRP) review of all the components of the guidelines is taking place. The final risk assessment guidelines will contain information from each of the Technical Support Documents, and will also undergo public and SRP review. In the end, the entire set of documents will have undergone public and peer review.

Comment: OEHHA should not direct limited resources toward developing new health values where USEPA values or other ARARs already exist.

OEHHA should focus their limited resources on developing appropriate supplemental risk assessment guidance for the areas explicitly addressed in SB 1731 (e.g., uncertainty analysis, exposure assessment). Development of exposure limits for assessing health risks for acute, chronic non-carcinogen, or carcinogen exposures should be deferred to U.S. EPA for application within specific state programs.

Response: The U.S.EPA has a limited number of cancer potency factors and chronic noncancer reference concentrations which we can use. To date, USEPA has not developed any acute reference concentrations for routine or planned releases. OEHHA has filled this void by developing acute Reference Exposure Levels for one-hour exposures.

As stated in the statute (Health and Safety Code Section 44306), "health risk assessment means a detailed comprehensive analysis prepared pursuant to Section 44361 to evaluate and predict the dispersion of hazardous substances in the environment and the potential for exposure of human populations and to assess and quantify both the individual and population-wide health risks associated with those levels of exposure." Health risk assessments require a number of inputs for risk characterization. Exposure assessment is only one of them and exposure information alone does not constitute a risk assessment. In order to characterize the risks from exposure one needs information on the toxicity of the chemicals emitted. The acute and chronic reference exposure levels for noncancer endpoints, and the cancer potency factors function as measures of the toxicity and are used quantitatively to assess health risks. Development and compilation of existing cancer potency factors and reference exposure levels is integral to the development of comprehensive risk assessment guidelines. Costs of developing the reference exposure levels and cancer potency factors were included in the cost estimations of SB 1731 legislation prepared for the legislature. It was therefore clear from the beginning that some effort was going into developing these toxicity criteria. U.S. EPA has neither the resources nor the mandate to address the chemicals subject to California's Air Toxics Hot Spots Act.

Comment: The guidelines establish values and methodologies that will be used in the risk assessment process. They also introduce risk management elements that will bias regulatory decision making. For example, in addressing Risk Characterization (Presentation of Results, pg. 12), OEHHA uses a hazard index of 0.5 as a trigger for evaluation of, and inclusion of, the potential additive health risk from background concentrations of criteria air pollutants for respiratory irritants. This provision is not mandated by AB 2588 or SB 1731 and would limit CARB and local district discretion in making cost-effective risk management decisions. Such initiatives should be addressed independently of the revised risk assessment guidelines to allow for full consideration of potential risk management implications (e.g., increase in a facility's risk above a district notification threshold due to the conservative default assumption of additive toxicity from background criteria air pollutants). It is critical that risk assessment and risk management activities be considered separately, so that informed regulatory decisions can be based on a full evaluation of all relevant factors. Therefore, we recommend that OEHHA remove all such risk management references from the draft. Of course, we recommend that subsequent

draft guidelines also observe this critical separation between risk assessment and risk management.

Response: The proposal to consider background levels of criteria air pollutants has been dropped.

Comment: The Executive Summary of the Technical Support Document (pg. iv) states that "The RELs also have application in characterizing health risks in event of unplanned releases." This statement suggests an inappropriate broadening of the applicability of these guidelines, which are being developed under legislative mandate for the express purpose of addressing the conduct of health risk assessments for facilities under the AB 2588 program. Such expansion of the guidelines' applicability beyond conducting AB 2588 risk assessments appears to exceed the legislative intent and authorization of SB 1731. In addition, given the questionable scientific basis of the animal data used to derive some of the REL values (see Appendix 1), it is clearly premature to contemplate broadening the regulatory applicability of the proposed RELs. Moreover, we are concerned that such statements may be cited inappropriately in tort litigation against facilities, as supporting exaggerated claims of adverse health effects simply because an REL may have been exceeded during an accidental release. Full consideration of the compounded conservatism in establishing RELs, particularly in the choice of "endpoints of toxicity" in the hazard identification phase, combined with the default application of ten-fold uncertainty factors, and the methodology proposed for addressing the relative contribution of concentration and time using a modification of Haber's Law in the dose-response phase, clearly leads to the conclusion that the resultant acute RELs are uniformly set at levels that are likely one or more orders of magnitude below exposures that actually result in injurious effects. We recommend that OEHHA strike this statement from the draft document, and add a precautionary statement which clearly addresses such inappropriate applications of the guidelines.

Response: The proposed acute Reference Exposure Levels were already under development prior to the passage of SB 1731. The effort to develop acute RELs was started in 1989 (under a different program in conjunction with California's Office of Emergency Services), and the guidance document thus produced was publicly reviewed in 1991. When SB 1731 was passed, we expanded our efforts to include evaluating exposures to routine emissions. OEHHA initially took the existing guidelines and modified them to fit the Air Toxics Hot Spots program risk assessment guidelines by developing RELs for one hour community exposures. OEHHA has since altered the document to emphasize its applicability in conducting risk assessments under AB 2588.

As part of our reevaluation of the acute RELs following public comment, OEHHA has analyzed the use of the benchmark concentration to reduce uncertainty and the magnitude of the uncertainty factors. Where data are adequate, we have used the benchmark concentration approach. The toxicological endpoint reflects the scientific literature and does not introduce "compounded conservatism". The application of default ten-fold uncertainty factors in a REL calculation accounts for the lack of scientific information (uncertainty) in extrapolating from animals to humans and the degree of interindividual variability in the human population. There are

no data to suggest that the RELs are set at levels "one or more orders of magnitude below exposures that actually result in injurious effects". It is because inadequate data are available that uncertainty factors are used. OEHHA is currently studying the degree of protection which 10-fold uncertainty factors afford.

Comment: Health based ambient air quality standards have been established for criteria air pollutants under federal and state ambient air quality programs. Under these programs, facilities must meet stringent criteria pollutant emission standards for existing equipment and any new or modified equipment. Inclusion of criteria air pollutants in the AB 2588 program (Table 1) will overlap efforts of ambient air quality programs. Such action will increase AB 2588 compliance costs and complicate the program without a corresponding improvement in human health and environmental protection. Criteria pollutants are not listed as hazardous air pollutants (HAPS) under Section 112 (42 USC section 7412(b)) and are therefore not required to be defined as a toxic air contaminant under state law. Criteria pollutants are not among the substances required to be quantified in the AB 2588 program. In addition, SO_2, NO_2, and ozone are not included in any of the substance lists in H&SC section 44321. In view of these facts, criteria pollutants should not be listed as toxic air contaminants.

Response: There has been no attempt at listing criteria air pollutants as toxic air contaminants. Since exposure occurs simultaneously to criteria air pollutants as well as hot spots chemicals emitted from a facility, from a scientific standpoint, evaluation of the health impacts from exposure to criteria air pollutants and hot spots emissions makes sense. In spite of this, consideration of background concentrations of criteria pollutants will not be required in the Hot Spots Program.

Comment: The guidelines provide examples of facility emissions that must be evaluated in the risk assessment, including venting to flares and pressure relief valves (pp. 4). The facility risk assessment mandated by the Legislature for the AB 2588 program applies specifically to impacts due to air releases that result from routine operation of a facility, or release that are "predictable". The above-referenced examples should include language clarifying that the guidelines are only applicable to routine or predictable facility emissions.

Response: Health and Safety Code Section 44303 defines "air releases" as "any activity that may cause the issuance of air contaminants, including the actual or potential spilling, leaking, pumping, pouring, emitting, emptying, discharging, injecting, escaping, leaching, dumping, or disposing of a substance into the ambient air and that results from the routine operation of a facility or that is predictable, including, but not limited to, continuous and intermittent releases and predictable process upsets or leaks." Venting to flares and pressure relief valves are predictable occurrences. Therefore, they should be included in evaluating health risks from facility emissions.

Comment: The AB 2588 program is intended to identify risks from individual facility emissions. In discussing the legislative intent of the AB 2588 program, H&SC section 44301 makes explicit

reference to "specific sources". Subsection (h) states: "it is in the public interest to ascertain and measure the amounts and types of hazardous releases from specific sources that may be exposing people to those releases, and to assess the health risks to those who are exposed." There is no legislative mandate to address multiple-facility impacts. OEHHA guidance should not overreach clear legislative intent. All references to requirements or recommendations associated with multiple facility impacts should be removed from the draft.

Response: H&SC section 44301 (d) states that toxic air releases "may create localized concentrations or air toxics "hot spots" where emissions from specific sources may expose individuals and population groups to elevated risks of adverse health effects, including, but not limited to, cancer and contribute to the cumulative health risks of emissions from other sources in the area." It is clear that the legislature is concerned about cumulative exposures. Based on this statement, a District at its discretion may do an analysis of multiple facility impacts and ask for information from facilities in order to conduct such an analysis. OEHHA never intended to imply that a facility operator do an assessment of the risks from neighboring facilities.

TECHNICAL COMMENTS:

The following comments specifically address the methodology used by OEHHA in developing the draft guidelines:

Comment: The use of uncertainty factors, and their magnitude, must take into account the severity of the effect against which the public is being protected. Particularly for Level I Acute Toxicity Exposure Limits (generally the REL), the endpoint on which the exposure limit is based is generally a mild effect of questionable toxicological significance (mild respiratory irritation, mild eye irritation, minimal signs of CNS depression). In many cases an uncertainty factor far less than 10 (e.g. 2-3) would provide adequate protection.

Response: OEHHA has modified its uncertainty factor methodology and now utilizes an uncertainty factor less than 10 under certain circumstances. For example, for benchmark concentration calculations, the interspecies uncertainty factor for animal studies and the intraspecies uncertainty factor for human studies has been changed to 3. Similarly, for sensory irritation, the uncertainty factor for LOAEL to NOAEL extrapolation has been reduced from 10 to 3.

Comment: An example of the inappropriate use of ten-fold uncertainty factors is provided in the calculation of the REL for methanol (REL = 2.1 ppm). Following exposure of 12 young, healthy men to 190 ppm for 75 minutes, two of 20 tests in a neurobehavioral/neurophysiological battery showed statistically significant effects. The two tests involved measured fatigue and concentration, and visual evoked potentials, both transient, questionable toxicological endpoints. In addition, while the effects were statistically significant, in both cases they were within the normal range of test values for subjects during sham exposures (Cook *et al*., 1991).

In determining the REL, OEHHA considered 190 ppm the LOAEL, and applied two ten-fold uncertainty factors; one to account for LOAEL-to-NOAEL conversion, and the second to account for "interspecies (intraspecies) variability." Following the application of Haber's Law to adjust from a 75 minute experimental exposure to a one-hour exposure limit, the REL (Level 1 Exposure Level) was determined to be 2.1 ppm. Given the minimal "effect" and questionable significance of the effects observed, it appears appropriate to use uncertainty factors far lower than ten.

Furthermore, we believe that the effects observed in this study, which serve as the basis for calculating the REL, do not constitute a LOAEL, and should be considered a NOAEL, thus eliminating the ten-fold uncertainty factor for conversion from LOAEL to NOAEL. It is also unlikely that intraspecies differences in sensitivity to such a non-specific endpoint (minimal signs of CNS depression) would span an order of magnitude (ten-fold uncertainty factor).

Response: OEHHA has revised its interpretation of the Cook *et al*. (1991) study; the exposure level reported in that study is considered to represent a NOAEL. No data is presented to document the magnitude of intraspecies variability, so the default uncertainty factor of 10 is used. The REL has been appropriately revised in the Technical Support Document from 2.8×10^3 to $2.8\ 10^4$ $\mu g/m^3$.

Comment: Finally, given the minimal "effect" on which the REL is based, including its questionable significance and transitory nature, it is prudent to re-evaluate the default application of a ten-fold uncertainty factor. In such a case, the minimal
severity and ready reversibility of the "toxic endpoint" against which the public is being protected suggest that the application of a much smaller uncertainty factor (e.g., two- to three-fold) would provide an adequate margin of error.

Response: OEHHA has defined specific criteria for using reduced uncertainty factors. The data do not indicate that a reduced uncertainty factor is warranted for central nervous system endpoints or for intraspecies variability in general. In fact, for compounds for which such data are available, human variability may range from 7-fold to several orders of magnitude (Horstman D *et al*., 1986; Hattis D, 1996). Furthermore, it is precisely because the effect is subclinical and reversible that it is considered a mild, not a severe, adverse effect. The REL is intended to protect against adverse effects and the REL for methanol is consistent with this purpose.

Comment: Note also that the Level III l-Hour Acute Toxicity Exposure Limit for methanol is 40 ppm. The accompanying text states: "Exposure to methanol above this level may result in death due to respiratory or cardiac arrest." While this statement is technically accurate exposure to methanol at some level, significantly above 40 ppm, would result in death due to respiratory or cardiac arrest; establishing the Level III Acute Exposure value at 40 ppm is clearly a gross overstatement of the acute hazard posed by this chemical. Furthermore, this Level III exposure limit is completely inconsistent with the current 8-hour TLV of 200 ppm. While we understand OEHHA's concerns relative to establishing RELs based on TLVs, the 8-hour TLV for methanol

of 200 ppm suggests that significant industry-sponsored exposure assessment data are available from routine industrial hygiene monitoring. This data suggests that significantly higher acute exposures are tolerated within the human population with no adverse effects.

Response: OEHHA agrees that the life-threatening level for methanol is overly conservative and has substituted the 1996 NIOSH IDLH value of 6,000 ppm (7860 mg/m^3).

Comment: Beyond the example cited above for methanol, routine, default application of a tenfold uncertainty factor is inappropriate for many of the 54 chemicals for which acute RELs are established in the draft guidance. Some endpoints of toxicity (e.g., respiratory irritation resulting from direct tissue damage from exposure to caustics) would be expected to produce a dose-response relationship that is essentially the same in all mammalian systems, and such chemicals are therefore particularly good examples of where the default application of a ten-fold uncertainty factor is inappropriate.

Response: OEHHA has defined specific criteria for the use of uncertainty factors less than 10, as outlined above. OEHHA encourages the commentator to submit data supporting factors for extrapolation for specific toxicological endpoints other than the factor of 10.

Comment: As cited above for methanol, there are a number of chemicals for which the selection of a "toxicologically significant" endpoint on which to base the establishment of an acute exposure limit is questionable. As has long been debated in the evaluation of chronic non-cancer endpoints, there are many effects that are observed following exposure to chemicals that are measurable, but which are not toxicologically significant, and merely reflect an adaptive response in the organism. The draft acute exposure guidance should be carefully reviewed to assure that the endpoints used as the basis for calculating RELs and/or Level I, II, or III Exposure Levels are appropriate for use as the basis of the hazard identification phase of acute health risk assessment.

Response: No specific examples of this concern or recommendations are given in the comment. However, OEHHA agrees that toxicologically significant endpoints should be used as the bases for the RELs and every effort has been made to ensure that this is the case. The identification of the critical endpoint and study are vital to determining a useful REL.

Comment: Historically, AB 2588 risk assessments evaluated only those chemicals with state approved health effects values. According to the draft (Part 1, pp. 7), facilities preparing risk assessments pursuant to AB 2588 would be required to quantify emissions and estimate potential acute health effects for all listed AB 2588 chemicals emitted by their operation, even for those chemicals for which OEHHA RELs and exposure levels have not been developed. Once health effects values, including acute RELs, have been developed, these chemicals will need to be evaluated at each step in the AB 2588 process. We are concerned that OEHHA has not fully considered the potential ramifications of their proposed "interim" REL process on existing AB 2588 programs.

Response: OEHHA has withdrawn this proposal.

Comment: Current regulations (approved by OAL 1/31/94) require that low, medium, and high priority (non-significant risk) facilities submit a Summary Update Form every four years. Part C of this form requires that the operator certify what changes, if any, have occurred since the last inventory period that contribute to facility risk. Currently, only those substances with state-approved health effects values are considered in evaluating facility risk. However, OEHHA's proposal suggests that all listed substances would need to be evaluated. This proposal could have a significant effect on facility risk between inventory updates, thereby necessitating a full inventory plan and report for many facilities. Recent agency/industry inventory streamlining efforts would be nullified.

Facility prioritization scores would need to be recalculated to evaluate emissions of all substances with health effects values. For some facilities (e.g., petroleum exploration & production) the number of substances could more than double. This change could drive many facilities, currently classified as low and medium priority, into a high priority classification, triggering risk assessment requirements.

Response: As new reference exposure levels are adopted, some facilities may need to provide more information. This does not nullify streamlining efforts. Concern that a facility might have to provide more inventory information or may need to be reprioritized should not prevent the development of reference exposure levels for listed substances.

Comment: As noted above, the calculated facility risk is assumed to increase under OEHHA's proposal. As a result, certain facilities may trigger existing action thresholds (e.g., notification). However, these thresholds reflect our current understanding of cumulative facility risk based on a limited universe of substances. By substantially expanding the universe of substances, we are changing the meaning of calculated risk. In addition, for substances with limited health effects data, facilities would have to develop overly conservative values that may substantially overstate risk estimates. Risk assessments would be based on data of grossly unequal quality.

OEHHA's "interim" REL proposal will also result in different facilities developing different values for the same chemical. It is not clear if, when, or how OEHHA might supplant "interim" values with a single state standard -- the draft guideline does not suggest a protocol for this purpose. However, it is clear that the proposed process will generate new information for many chemicals on a continuous basis. We are concerned that OEHHA may use this information to adjust RELs on a continuous basis. Such action would place an inordinate administrative burden on facilities, districts and the state. For example, facilities would be compelled to continually update emissions inventories and HRAs to reflect the most current data. The cost and time associated with conducting risk assessments would increase dramatically. Moreover, the draft acute guidelines do not discuss the process by which OEHHA will approve interim RELs. This process will should be developed before facilities are required to calculate their own RELs.

Clearly, OEHHA's "interim" REL proposal must be subject to a thorough cost-benefit analysis before it is implemented.

The Proposed "Interim" REL Process Should be Compatible With OEHHA's Statutory Requirements for Evaluating Health Effects.

All New or Updated Health Effects Values Should be Subject to Standard Public and Peer Review Processes.

Response: OEHHA agrees with the comment. As stated above, the proposal for "Interim RELs" has been withdrawn. All updates of RELs are subject to public and peer review.

Comment: In determining the applicability of federal MACT standards, Section 112 General Provisions require that facilities evaluate only emissions of substances for which EPA has assigned appropriate and relevant health values. For example, in determining whether a facility is a "major source" of emissions, E&P facilities are required to evaluate emissions of 16 chemicals. The guidelines should reflect federal policy, or clearly justify the need for a more stringent approach based on human health and environmental benefit (AB 1144, AB 969, SB 1082).

Response: The Air Toxics Hot Spots program is designed to evaluate emissions of a specified list of substances. What the federal government does under separate statutes and for different purposes does not affect the implementation of the Hot Spots Act. Thus, we are evaluating health effects of many of the chemicals listed in the Air Toxics Hot Spots list of substances.

Comment: The requirement for consideration of "background concentrations" of criteria air pollutants is beyond the scope of AB 2588 and should be removed from the guidelines. Historically, AB 2588 focused on health risks associated with individual facility emissions. The draft requires that facilities also include background concentrations of criteria pollutant emissions in their risk assessments if the acute hazard index for their corresponding toxic endpoint is greater than 0.5 (pp. 13). This is not appropriate because source concentrations of criteria pollutant emissions have already been accounted for in the risk assessment. In addition, the toxic components of source criteria emissions are accounted for in the risk assessment. Evaluating background concentrations in addition to source concentrations will effectively double count facility emissions.

Given contributions from other stationary, area and mobile sources, consideration of background concentrations could subject a facility to more stringent regulatory requirements due to emissions that are beyond the control of that facility. For example, consideration of background concentrations could raise a facilities' hazard index level above 1, triggering public notification requirements in most districts. Consideration of background concentrations will also substantially increase facility administrative burden associated with the risk assessment process. For example, facilities could be required to evaluate their impact to receptors located in areas where their 0.5

HI isopleths overlap those of surrounding facilities. The proposed requirement for consideration of "background concentrations" of criteria air pollutants must be subject to a thorough cost-benefit analysis before it is implemented.

Response: OEHHA has withdrawn the proposal to include background criteria air pollutants in the risk assessment. Historically, background criteria air pollutant concentrations have been included in some AB 2588 risk assessments in evaluating the hazard index for respiratory irritation. The facility's emissions of criteria air pollutants have not been included in the risk assessment. Furthermore, no districts have used background criteria air pollutant contributions as a trigger for notification.

Comment: Any hazard identification information that has not been developed and provided by OEHHA should not be required. The draft guideline requires that risk assessors provide information, when HI exceeds 0.5, for emitted chemicals that can impact a particular health endpoint but which are not included in the HI calculation. To assure consistency among risk assessments, and to minimize costs, such information should not be required. Providing supplemental information should be an option exercised at the facilities' discretion.

Response: OEHHA has withdrawn the proposal to provide information for hazard indices above 0.5.

Comment: Reference Exposure Levels for many chemicals are, understandably, based on toxicity studies conducted in laboratory animals, with NOAELs adjusted by ten-fold uncertainty factors to account for potential interspecies and intraspecies differences. In most cases, the resultant RELs are much more stringent than current occupational exposure limits supported by health effects data in exposed humans. In such cases, particularly where occupational exposure data have been collected, but not reviewed by OEHHA, RELs derived from occupational exposure data should be directly applicable to human health effects endpoints with only the potential application of an uncertainty factor (of appropriate magnitude) to account for potential intraspecies variability within the human population.

Response: It is inappropriate to directly compare or attempt to use occupational standards for the general populace. Where occupational exposure data represent the best available toxicological data, we would use these data. Very often, occupational standards are not based on rigorously examined epidemiological data, but appear to be anecdotal in nature.

Comment: Appendix 1 contains a review of the OEHHA methodology used to derive RELs. This review was prepared by a third party consultant on WSPA's behalf. Comments are provided on the general selection of data used to derive RELs, use of a modification of Haber's Law in the process, and use of the Benchmark Dose approach. An alternative method for deriving acute RELs that may merit further discussion is also provided as an attachment to Appendix l.

Appendix 1 contains a review of the methodology applied by OEHHA to establish RELs for several specific chemicals. A critical review of the methodology used to establish RELs for five chemicals of clear significance to our industry are included as Appendix 1. However, the omission of additional chemicals should not be perceived as concurrence with the methodology applied by OEHHA. In addition to the chemicals addressed in Appendix 1, each of the remaining 49 chemicals should be peer reviewed in a similar fashion by an independent reviewer, outside of Cal EPA. The following five chemicals were reviewed by a third party consultant (ICF Kaiser Engineering, Inc., Ruston, LA) on WSPA's behalf:

- Benzene
- Toluene
- Hydrogen Sulfide
- Ammonia
- Nickel

Response: See responses to specific technical comments by ICF-Kaiser, below.

Comment: Revisions to the process of conducting health risk assessments under the AB 2588 Program should be focused on improving the process and reducing uncertainty. Therefore, for many of the chemicals for which acute RELs are either proposed or planned, it is critical that OEHHA identify data gaps for each specific chemical evaluated to identify where resources are best spent on strengthening the data upon which acute RELs are based. Before setting such strict exposure limits as proposed in the draft acute guidelines, OEHHA should clearly identify data gaps for each chemical that, once filled, will substantially reduce the identified uncertainty, thereby allowing for more accurate prediction of risk and more scientifically defensible exposure limits. Consistent with this reduction in the uncertainty surrounding health risk assessments, OEHHA's draft guidelines should clearly identify a process for incorporation of additional scientific data to reduce the uncertainty surrounding the development of acute exposure levels (including the REL) for use in the AB 2588 risk assessment process.

Response: The REL development process uses an iterative approach. Review by the regulated community provides opportunity for submission of further scientific data. If the commentator has data to submit regarding specific chemicals, OEHHA will review the data. Additionally, OEHHA plans to update the RELs on an on-going basis. All updates will undergo public comment and independent review by ARB's Scientific Review Panel.

References:

Horstman D, Roger LJ, Kehrl H, Hazucha M. Airway sensitivity of asthmatics to sulfur dioxide. Toxicol Indus Health 1986; 2:289-298.

Hattis D. Variability in susceptibility-how big, how often, for what responses to what agents? Environ Toxicol Pharmacol 1996; 2:135-145.

OEHHA Responses to Comments Received from ICF-Kaiser (for WSPA)

Comment: For some of the Level II concentrations, OEHHA has relied on the results of reproductive/developmental studies, in which the animals were exposed repeatedly, in some instances for the duration of gestation. OEHHA has characterized Level II as protective against "disability" due to immediate effects, such as loss of consciousness or cardiac or respiratory effects, and to other, potentially delayed health effects, such as hepatitis or reproductive and developmental effects. Development of a one-hour limit intended to be protective against potential delayed effects without consideration of the mechanism of that effect is highly questionable. The potential for these delayed effects to develop following a one-hour exposure should be evaluated only in studies with a single exposure of a similar duration. Once the duration of exposure has exceeded 24 hours or exposure is repeated for several days, mechanisms of toxicity may come into play, such that Haber's Law no longer applies making the incidence of certain endpoints, such as reproductive /developmental effects, highly unlikely to occur as a result of a one-hour exposure, even at high exposure levels.

Response: While it is true that 1-hour exposure data might be useful for developing RELs based on reproductive and developmental (R/D) toxicity, such data do not exist. One would have to conduct studies in which each hour of gestation were studied separately, which is logistically impractical. Therefore, since it is reasonable to assume that R/D toxicity can occur in humans following a single exposure to a chemical with demonstrated R/D toxicity in animals, we are constrained to use the animal data available. This is what we have done in the Technical Support Document. Since there is no assumption-free mechanism to incorporate such data into human health risk assessment for acute exposures, OEHHA has adopted a scientifically-defensible and not an extreme set of assumptions.

First, we have proposed consideration of the day of exposure as the base unit for onset of R/D effects. Within the unit exposure day, OEHHA has proposed time-extrapolation to approximate an equivalent daily 1-hour exposure. It is commonly accepted that exposures to chemicals during brief, critical periods of gestation may result in R/D effects. For this reason, OEHHA considers each daily exposure to be an independent event. This assumption is obviously more valid for chemicals that do not bioaccumulate or do not have cumulative toxicity. A more sophisticated treatment of chemicals that accumulate and have some degree of cumulative toxicity is warranted but is not feasible at this time. Therefore, OEHHA has assumed that recovery between successive exposures has been achieved by the experimental animals. To assume otherwise in absence of specific data would not be health protective and would be unjustifiable both scientifically and from a public health standpoint.

For these reasons, OEHHA can not accept the suggestion in the comment that the least health-protective assumption should be used, namely assuming complete additivity of all doses received by experimental animals in order to achieve a R/D effect.

Comment: In general, when the NOAEL approach is used, if multiple NOAELs are available in one animal species, then the highest NOAEL for that animal species is used in comparison to

other species NOAELs. The highest NOAEL that is lower than the lowest LOAEL is generally selected based on a comparison of the best quality studies as the NOAEL upon which to base an exposure level, because this ensures that the exposure level is based on the most sensitive endpoint. Selecting the highest NOAEL, as indicated by OEHHA, may not be protective for the most sensitive endpoint.

If the NOAEL approach is used, which is not the most appropriate methodology for deriving a one-hour exposure level, the NOAEL approach recommended by OEHHA may be less conservative than that currently recommended by the USEPA. By selecting the highest NOAEL without considering the lowest LOAEL, OEHHA approach is less conservative, which may result in a level that is not protective of the most sensitive endpoint. The types of problems encountered in defining a NOAEL can be eliminated by using the BMD approach.

Response: No specific examples are given in the comment to support these concerns. We believe that the NOAEL approach used in the Technical Support Document is fully consistent with the intent of the uncertainty factor methodology used by USEPA. It should be recognized that USEPA does not presently have any acute non-cancer reference values for routine release scenarios or corresponding methods to use for comparison.

The comment recommends using benchmark methodology in place of the NOAEL approach. Where possible, OEHHA has proposed benchmark concentration methodology for determining 1-hour exposure levels. However, most data sets do not allow for quantal dose-response benchmarks to be determined. Benchmark methodology for continuous data is being examined, but is not currently available.

Comment: An attempt should be made to develop an exponent based on the empirical data available from acute inhalation toxicity experiments, rather than attempting to use a default value for n. . . .

The analyses conducted by Ten Berge *et al*. (1986) examined the relationship between concentration and exposure time for predicting mortality response. OEHHA used the chemical-specific regression coefficients (n) reported by Ten Berge *et al*. (1986), when available, to adjust concentrations administered to humans or animals in the study selected for a duration different than one-hour. However, because these regression coefficients were derived based on mortality data, they are not applicable to other endpoints. . . .

OEHHA has apparently chosen to use a default approach, rather than consider mechanistic data or in the absence of such data, a conservative approach designed to mitigate potential overestimation of exposure concentrations. If so, that should be stated openly rather than attempting an ad hoc scientific justification based on Ten Berge *et al*. (1986).

Response: The comment expresses disagreement with the use of a default procedure for estimating 1-hour concentrations that cause adverse effects. It is correct that the Ten Berge *et al.* (1986) paper used mortality data to derive exponents of "n" for the equation $C^n \times T = \text{constant}$.

OEHHA uses the principle of the Ten Berge *et al*. paper without necessarily using specific values contained in the paper. OEHHA agrees with the comment that mortality data do not necessarily reflect the dose-duration response relationships for other endpoints. When specific data on the endpoints of concern existed to derive the exponential term for this relationship, we have used the data and derived "n" (see chlorine, ammonia, and phosgene as examples). The generic example given in the comment for using "mechanistic data" to derive the exponential term when response data do not exist describes differences between systemically and locally acting irritants and the usefulness of considering different mechanisms when deriving "n". While the example given contains no specific data or citations, it does point out the importance of considering biological mechanisms. The comment advocates the exchange of default values for the assumption that mechanistic information is an adequate substitute for actual exposure data. This comment overestimates the quantity and utility of "mechanistic" data for such acute exposures. Furthermore, no specific recommendations are made in the comment on how such information can be used consistently and quantitatively in estimating the exponential term.

OEHHA has derived acute exposure levels by methods that we believe are scientifically sound and based on existing data. Because data gaps exist, health-protective parameters are used. If data should become available that suggest changes to this methodology or to specific values, we will consider such data. Mechanistic data may be of use in estimating exponential terms for the modified Haber's Law. However, use of such data can only produce estimates, which should be validated by actual exposure data. Until methodology exists for the incorporation of such data, we believe that the use of the health-protective values are justified.

Comment: There is no factual basis for the statement that, 'For acute toxicity data, the log-probit model usually provides a good fit and is generally used.'

Response: The log-normal model is among the most widespread models used for toxicity testing and has traditionally been used extensively for determination of acute lethality and other dichotomous responses (Finney *et al*., 1971; Rees and Hattis, 1994). Furthermore, the log-normal distribution aspect of the model is biologically plausible and accounts for some degree of inter-individual variability (Rees and Hattis, 1994).

Comment: OEHHA's decision to define the BMD as a probability of a 1% response will always result in more stringent standards than the use of the NOAEL approach, resulting in an overly conservative approach. In a study by Allen *et al*. (1994) the experimentally derived NOAEL was compared to the BMD. Based on the work of Allen *et al*. (1994), of BMDs defined as a 10%, 5%, or 1% probability of a response based on quantal data, the 10% BMD level on average was closest to the NOAEL derived from the experimental data. A BMD level for quantal data based on a 1% probability of a response was on an average of 29 times lower than the NOAEL, while at the 10% probability level, the average BMD level was 3 times lower than the NOAEL. Therefore, it appears that the proposed guidance using the BMD approach will in general result in lower levels than the NOAEL approach and will be highly conservative. An estimate of exposure producing a 1% probability of response may be model dependent; however if a higher response

level, such as 10%, was used, the BMD would be less model dependent. Therefore, if the BMD approach is to be used for the development of acute exposure levels, OEHHA's BMD should be defined as a probability of a 10% response, rather than a 1% response.

Response: Although our analysis shows that there is not much difference between the BC_{01} and the BC_{05}, in order to be consistent with USEPA, OEHHA has changed the proposed benchmark from 1% to 5%.

It is not the goal of the benchmark dose approach to emulate results from the NOAEL approach, and the continued reliance on such comparisons is inherently flawed. Furthermore, the data upon which the comment relies is an analysis of developmental data sets by Allen *et al*. (1994). In their analysis, Allen *et al*. show that BC_{01} is 29-fold below the level of the NOAEL, on average. The BC_{05} values were also below the NOAEL, on average, by about 6-fold. However, the analysis is extremely limited due to the examination of only developmental toxicity studies. In our analyses, the BC_{01} is less than 2-fold below NOAELs taken from acute studies, and only about 1.3-fold below the BC_{05}, on average, for acute responses other than developmental defects. The dose-response slope for developmental toxicity studies may not be representative for all other endpoints. It is therefore premature to conclude that the BC_{01} values are overly conservative based on the analysis by Allen *et al*. (1994).

Comment: OEHHA recommends that when using the BMD approach uncertainty factors of 10 be applied to the BMD for uncertainty involved in animal to human extrapolation and human intraspecies variability. However, because the BMD approach takes into account intraindividual variability, which is what determines the shape of the dose response, OEHHA recommends adjustments resulting in factors of less than 10. This recommendation has merit, but it should not be a rigid default recommendation, like the modifying factor of 0.3 recommended by OEHHA. The biological aspects of the response should regulate the magnitude of the uncertainty factors and/or modifying factors used, rather than setting a default value.

Response: OEHHA agrees that if "biological aspects of the response" can be specifically quantified, they should be incorporated into uncertainty factors and the existing value should be replaced. However, this needs to be determined according to the individual chemical. The comment presents no data or examples that pertain to this process.

Instead of a modifying factor of 0.3, the REL development methodology now specifies an uncertainty factor of 3 to extrapolate from a LOAEL to a NOAEL for mild sensory irritation.

Comment: The preferred approach for the derivation of acute toxicity levels based on studies of longer duration is a method similar to the method reported by Guth and associates (1991) in Appendix D of OEHHA's Technical Document.

Response: The methodology proposed by Guth and associates in 1991 and suggested in the comment has potential applications that may make it the preferred one under some circumstances.

It allows the information from a large number of smaller studies reporting NOAEL or LOAEL data to be combined, therefore strengthening the conclusions reached. However, because it has not yet been approved for use by USEPA and because it is useful only for chemicals on which there are a large number of studies, it is not a recommended approach for the development of reference exposure levels.

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Rees DC, Hattis D. Developing quantitative strategies for animal to human extrapolation. In: Hayes AW, editor. Principles and methods of toxicology. 3rd ed. New York: Raven Press; 1994.

Chemical-Specific Comments

Comment: For the Level I concentration, OEHHA used a regression coefficient, n, of 4.6 reported in Ten Berge *et al*. (1986). However, this regression coefficient (n) is based on a dose-response relationship for mortality. The use of any value based on mortality data is not usable for extrapolation to other endpoints, especially for nonsystemic endpoints, such as irritation.

Response: The comment incorrectly concludes that OEHHA used Ten Berge *et al*. (1986) mortality data to arrive at the exponential term of 4.6 for the time-extrapolation used in the benchmark calculation. In fact, as stated in the ammonia summary,

> The value for the exponent n was empirically derived from the preceding data sets [Industrial Biotest Laboratories, 1973; MacEwen *et al*., 1970; Silverman *et al*., 1949; Verberk, 1977]. The value of n (in the formula $C^n * T = K$) was sequentially varied for the log-normal probit relationship analysis. Using a chi-square analysis, a value of n = 4.6 was found to be the best fit.

OEHHA therefore derived the exponential term of 4.6 using human irritation data and maximizing the goodness of fit in a series of log-normal regressions. The value reported by Ten Berge *et al*. (1986) for ammonia is 2, not 4.6, and is unrelated to the OEHHA value.

Comment: OEHHA used the Haber's Law modification to extrapolate a one-hour concentration for the data from four studies with human irritation or "nuisance" as the endpoint and then incorporated all incidence data from the four studies into the BMD model. Normally, when the BMD approach is used, studies are evaluated to select data sets for the BMD model. All applicable data sets are then modeled individually and the data set with the best fit is generally selected for the final decision of the BMD. Other factors play a role in the selection of the BMD, such as endpoints that are most relevant to human health. In general, individual data sets from individual studies are not combined and modeled simultaneously. If the protocols of the individual studies are identical, the incidence data may be grouped and modeled together as one data set. However, the protocols from the four studies used by OEHHA for the development of

the Level I REL were different. In addition, there were no control groups in any of the studies evaluated; therefore, the background in the BMD approach was assumed to be zero. Based on these considerations, the relevance of the Level I REL based on the BMD approach may be questionable. The incidence data from each of the studies considered should be modeled individually for the selection of the BMD.

Response: OEHHA derived an REL for ammonia using combined data from the 4 studies mentioned above. We believe, in this case, incorporation of several sets of human data into a single analysis better represents the human response to ammonia exposure. The 4 studies selected by OEHHA were of similar quality and experimental design. However, each was somewhat limited due to small sample sizes and number of exposure groups tested. The OEHHA analysis integrates 4 data sets in order to utilize the available data to the greatest extent, thereby decreasing uncertainty in developing an REL. The comment previously recommended a form of BC analysis by Guth *et al*. (1991) that combines not only studies with different protocols, but with vastly different durations, subject groups, species and severity.

Comment: OEHHA calculated the 1-hour Level I REL assuming that the LOAEL for decreases in lymphocytes and the host resistance resulted from 6 hours of exposure to 30 ppm benzene. However, based on the information reported the decrease in T-cells and B-cells was associated with 30 hours of exposure (6 hours/day for 5 days), while the decrease in host resistance was associated with 54 hours of exposure (6 hours/day for 9 days). Therefore, the derivation of an exposure level based on 6 hours of exposure in inappropriate, as well as the assumption that the effects were observed following the same duration of exposure.

Response: The comment raises the criticism that OEHHA should not use repeated dose studies of greater than 1-day for use in estimating 1-hour exposure levels. The comment is correct that the Rosenthal and Snyder study involved 6-hour, daily exposures for several days, after which the animals were killed and immunological parameters were measured. The comment recommends that full additivity of the intermittent daily doses be assumed by OEHHA for the exposure of the mice in this study. However, such an assumption is not necessarily valid scientifically, since some degree of recovery likely occurs during the 18-hour periods of benzene-free air the animals experienced between the 6-hour benzene exposures. Similarly, such an assumption is not public health protective when considering the uncertainties involved. Since measurements were not performed by the authors after single 6-hour exposures, the point cannot be proven either way, and OEHHA has chosen the more health-protective assumption in this case.

Comment: The relevance of an exposure concentration based on an immunological endpoint from a single study for use in drawing conclusions with regard to human immunotoxicity may be questionable.

Response: Animal immunotoxicity data are applicable to humans. Due to the highly conserved nature of the immune system across many species, animals are very likely appropriate surrogates for humans. In addition, immunotoxicity has been repeatedly linked with disease-resistance

deficits in many animal studies, and is used by the National Toxicology Program and several pharmaceutical companies as part of routine toxicity testing. The argument that immunotoxic effects in animals do not apply to humans is no longer valid. Finally, a compound with such well-documented hematopoietic toxicity in animals and humans as benzene has more than sufficient mechanistic evidence to support concern for immunotoxicity.

Comment: OEHHA reported that the Level II concentration for benzene was based on three studies, Coate *et al*. (1984), Kuna and Kapp (1981), and Keller and Snyder (1988). . . . OEHHA calculated the 1-hour Level II concentration based on the development of effects following the 4 hours of exposure; however, the animals were exposed for 60 hours (6 hours/day on days 6-15 of gestation).

Response: The severe adverse effect level value for benzene is based on the developmental toxicity study in rats by Coate *et al*. (1984). The comment incorrectly states that OEHHA based the severe adverse effect level on effects following a 4-hour exposure. OEHHA based the calculation of the severe adverse effect level on the 6-hour per day exposure duration in the Coate *et al*. (1984) study. For the same reasons as discussed above, the assumption of complete additivity for all exposures, as suggested in the comment, was not made by OEHHA.

Comment: Clear justification for the selection of 40 ppm as the NOAEL is not provided. Of the three studies evaluated by OEHHA for the development of the Level II criteria, the lowest NOAELs were reported by Keller and Snyder (1988) and Kuna and Kapp (1981). In this study, OEHHA reported that Keller and Snyder (1988) found suppression of erythropoietic precursor cells and persistent, enhanced granulopoiesis in the offspring of mice exposed to 20 ppm benzene on days 6-15 of gestation, with no hematotoxicity observed following exposure to 10 ppm benzene. In the Kuna and Kapp (1981) study, exposure to 50 ppm benzene resulted in reduced fetal weights, while no fetal effects were reported following exposure to 10 ppm benzene. These NOAELs are lower than the NOAEL of 40 ppm benzene for decreased fetal weights reported in rats following exposure for 6 hours/days on days 6-15 of gestation. The endpoints of hematotoxicity in the offspring of mice reported by Keller and Snyder (1988) would represent the most sensitive endpoint in the most sensitive species. However, the results of this study are not regarded as definitive due to limitations including small group size, lack of a dose-response relationship, and a lack of control results. OEHHA's reason for using the NOAEL from Coate *et al*. (1984) rather than the NOAELs of 10 ppm reported by Kuna and Kapp (1981) and Keller and Snyder (1988) is unclear. If the basis of OEHHA Level II concentration is just the Coate *et al*. (1984) study, OEHHA should not have included Keller and Snyder (1988) and Kuna and Kapp (1981) as part of the basis of their Level II concentration.

Response: The effects reported in the Keller and Snyder (1988) paper were, as stated by the commentator, "not definitive due to small sample size, lack of a dose-response, and a lack of control results." It is therefore unclear why the commentator proceeds to suggest the use of the Keller and Snyder (1988) study as the basis for the severe adverse effect level. OEHHA included discussion of these studies to illustrate the presence of other developmental toxicity results at

concentrations near to that reported in the Coate *et al*. (1984) study. Consistent with the methods proposed by OEHHA, the selection of the highest reported NOAEL below a LOAEL was used as the basis for the Level II for benzene. The studies by Kuna and Kapp (1981) and Keller and Snyder (1988) were examined by OEHHA and were found to contain either higher LOAELs or lower NOAELs than that seen in the Coate *et al*. (1984) study. The commentator is therefore correct (page 15 of attachment) that these studies contain lower NOAELs for developmental effects. However, according to the proposed methodology, it is the highest NOAEL below a LOAEL that should be selected to avoid being overly conservative.

Comment: Selection of the Level I REL for hydrogen sulfide illustrates a limitation in the OEHHA methodology-- a lack of clear guidelines for the selection of the study or endpoint upon which to base the one-hour level. The proposed LEVEL I REL for hydrogen sulfide is 0.03 ppm based on the perceived odor threshold in 16 individuals exposed to increasing concentrations of hydrogen sulfide for an unspecified duration.

Response: The REL for hydrogen sulfide has been recalculated based on the respiratory effects observed in the study by Jappinen *et al*. (1990). The REL has thus been changed from 42 to 140 µg/m³.

Comment: The commentator provides several criticisms of OEHHA's REL for nickel based on immunotoxicity in mice exposed to soluble nickel chloride.

Response: The new REL for nickel is no longer based on immunotoxicity in mice, but on small decrements in airway function tests in a study of human asthmatics.

Comment: OEHHA calculated their one-hour concentration [for toluene] assuming only 6 hours of exposure to the animals during gestation. However, the results indicate that the animals could be exposed for approximately the entire gestation period, with no fetotoxic effects on the offspring. If a one-hour concentration were calculated using this study, exposure would be for at least 120 hours, assuming that the exposure during gestation was the only contributing exposure period to the fetotoxic effects observed following exposure to 2000 ppm (the higher concentration). If 120 hours of exposure were considered, using the modification of Haber's Law would result in a one-hour concentration of 5477 ppm toluene. However, . . . the use of a study of this duration to determine a one-hour exposure is questionable.

Response: OEHHA acknowledges that the time-extrapolation from multiple exposures to a 1-hour exposure is not ideal. However, for a number of substances tested in developmental toxicity research, it has been shown that exposure to a dose of chemical during a critical period of development can result in adverse development of the fetus (e.g., in the case of thalidomide). Thus, unless information is available to the contrary for the chemical in question, it is prudent to assume that a single exposure to a teratogen may result in adverse developmental outcome. This being the case and since virtually all available reproductive/developmental studies are repeated

exposure studies, a single daily dosage is therefore thought to be sufficient for the occurrence of developmental toxicity.

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